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DIABETES MELLITUS—PROBLEMS OF PRESENT-DAY TREATMENT.*

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At the present time about 2000 diabetes deaths are registered annually in New York City, and the diabetes death rate is about 50 per cent higher than it was only 20 years ago. Approximately the same condition exists in all the large cities of the United States and more or less throughout the civilized world. A brief analysis of these facts, and possible remedial measures for them, are given in this paper.

Statistics. Chart I shows that for persons of both sexes the diabetes death rate in New York City has risen from 2.2 per 100,000 of population in 1871, to 29.3 in 1932. The total number of deaths has risen from 25 in 1871, to 2116 in 1932. A distinct rise in the number of diabetes deaths is registered not only in New York City but throughout the United States, as shown by the mortality statistics from other cities.

The death rate for males and for females was almost the same up to 1905, but thereafter the rates for the two sexes diverge—that for females rising more sharply, so that by 1932 the rate for females

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was about double that for males. The same change in trend about 1900 is noted in the individual age groups, as will be shown subsequently.

It should be understood that the term "diabetes death rate" is really only a record of death of persons who have had diabetes mellitus and is not a true indication of the deaths actually caused by that disease. In a sense, it reflects the incidence of diabetes. Diabetes is usually, though not always, given preference as the cause of death which is officially recorded when more than one condition is mentioned on the death certificate.

CHART I.

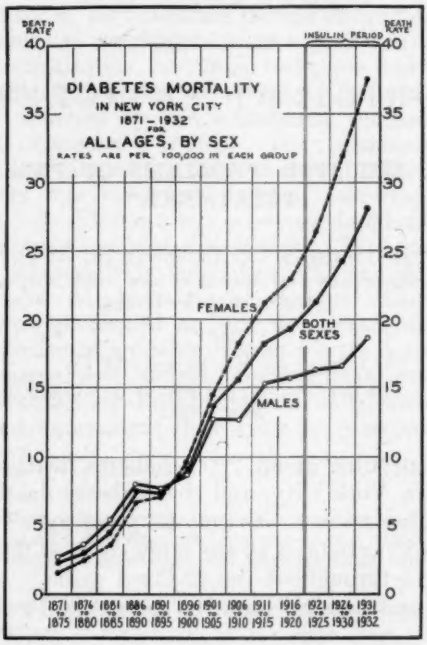
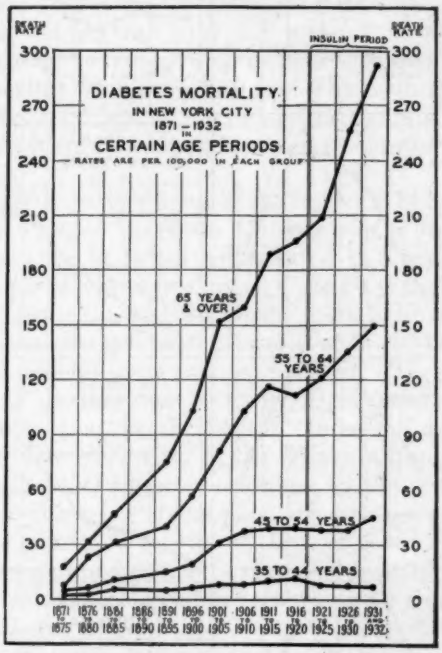


Chart II, and the rising scale for the death rate in the graphs of Chart III, furnish ample evidence of the increasing prevalence of diabetes in the older age periods. There are certain additional facts to be deduced from Charts II and III. A change in the trend of the mortality rate occurs in nearly all age groups about 1900. The most probable explanation of this fact is the introduction of the international classification of the causes of death by the Department of Health of New York City in 1901; this system of recording deaths has been followed from that time on, and consequently the statistics in regard to New York City are only strictly comparable from year to year since 1901.

We have presented the mortality statistics for New York City from 1870 to 1932 but warn against any reliance whatever being placed on the statistics prior to 1901. Diabetes was formerly regarded as a rare disease, but our study has convinced us that this was largely due to the inaccuracy and the rarity of urine examinations a few decades ago. Prior to about 1850, the presence of sugar in the urine was usually detected only by taste, or by sugar crystals obtained by evaporating the urine. Trommer's test was first described in 1841, and Fehling's test in 1848. A study of the medical histories of so efficient an institution as the New York

CHART II.

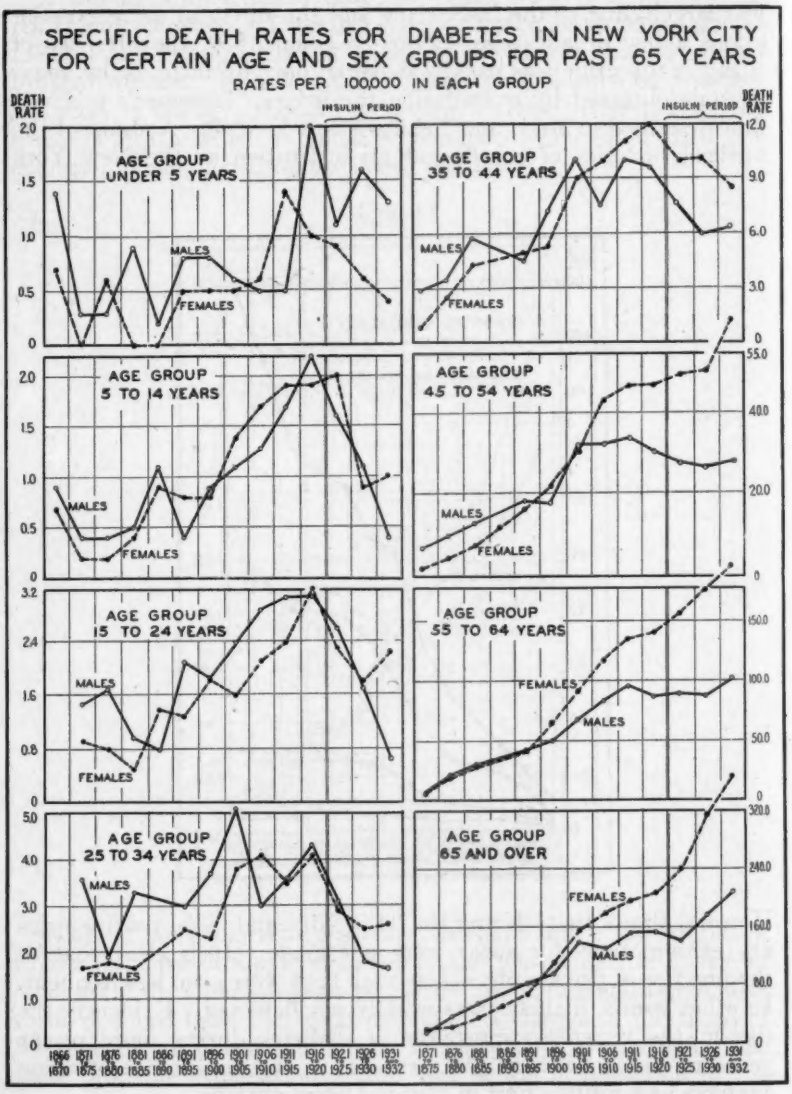


Hospital shows that, during the '60's, '70's and '80's, routine urinary examinations for sugar were not made. It is clear that in the practice of private physicians such tests were even less frequent. In other words, diabetes was usually not detected. Evidently the rise in the registered mortality of diabetes during more recent years is due, to a very great extent, to the acceptance of urine analyses as a routine part of physical examinations.

After 1920 there is a marked improvement in the death rate in females under 45 and in males under 65 years of age (Chart III). This may be definitely attributed to the effective use of insulin. In women over 45 years (Chart III) the rise in the death rate con-

tinues its previous upward trend in spite of insulin, while in men this is true only in the age group of 65 years and over. This increase

CHART III.


SPECIFIC DEATH RATES FOR DIABETES IN NEW YORK CITY
FOR CERTAIN AGE AND SEX GROUPS FOR PAST 65 YEARS
RATES PER 100,000 IN EACH GROUP
DEATH RATE
INSULIN PERIOD
AGE GROUP UNDER 5 YEARS
AGE GROUP 35 TO 44 YEARS
AGE GROUP 5 TO 14 YEARS
AGE GROUP 45 TO 54 YEARS
AGE GROUP 15 TO 24 YEARS
AGE GROUP 55 TO 64 YEARS
AGE GROUP 25 TO 34 YEARS
AGE GROUP 65 AND OVER
MALES
FEMALES

in diabetes deaths of older females is so great that it outweighs the favorable influence of insulin in the other age and sex groups and results in a distinct rise of the diabetes mortality as a whole.

It is true that physical examinations are more frequent and more thorough than they were a few years ago. This produces an apparent rise of the diabetes mortality rate. The data concerning this disease, obtained from 24 hospitals in New York City for the year 1931 by Dr. Alice Paulsen, shows that much remains to be accomplished in this direction; of 1617 cases of diabetes treated in these institutions, 318 (19 per cent) were diagnosed only after admission to the wards for the treatment of some other ailment. The greatly increased number of applications for life insurance by women and their more frequent participation in business activities, both entailing medical examinations, undoubtedly are factors which add to the recorded prevalence of diabetes in this sex during recent years. Inquiry of several large life insurance companies shows that the percentage of women among those examined for life insurance in the so-called "ordinary" business (with medical examinations including urine tests) has about trebled in the past 30 years and women policyholders now constitute a considerable proportion of the whole.

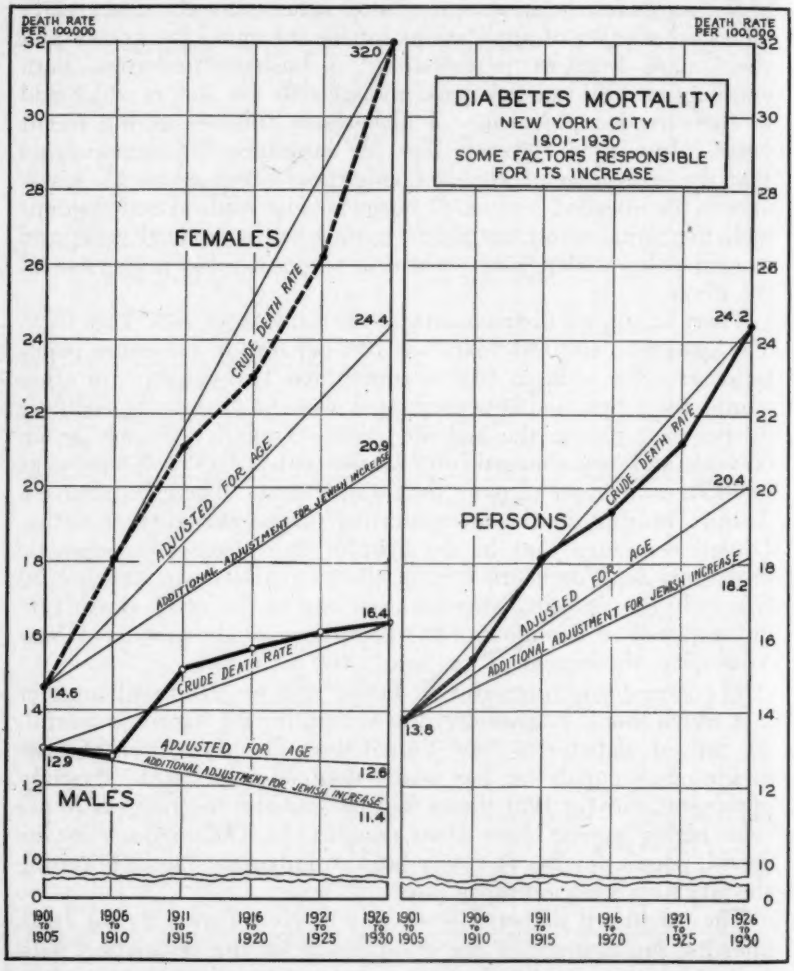
There has been a distinct aging of the residents in New York City. The age group 45 to 64 years was 13.1 per cent of the entire population in 1900, while in 1930 it constituted 17.3 per cent; in other words, the proportion of persons aged 45 to 64 years increased over 32 per cent during the last 30 years. Similarly, the age group 65 years and over changed from 2.8 per cent in 1900 to 3.8 per cent in 1930; an increase of more than 35 per cent. These facts have a distinct bearing on the interpretation of the mortality statistics. Drolet[1] computes that in the light of these figures the diabetic death rate for New York City in the 30 years from 1900 to 1930 rose only 58 per cent, whereas according to the crude death rate not adjusted to the aging of the population or the growth of New York City, the increment was nearly 100 per cent.

The large Jewish immigration during 1900 to 1915 is still another fact which should be considered in accounting for the rising mortality rate of diabetes in New York City. The proportion of Jews in the city's population has nearly doubled since 1900. A study of the statistics for 1931 shows that the diabetes mortality is 75 per cent higher among Jews than non-Jews.[2] The increase in the Jewish population has therefore been an important factor in raising the city's diabetes mortality rate.

The calculated diabetes death rate in New York City for 1930, allowing for changes in the composition of the population with respect to the age distribution and the proportion of Jews since 1900, is shown in Chart IV. The elevation of the total diabetes mortality during 30 years is only from 13.8 to 18.2, instead of 24.4 per 100,000. This reduces the rise calling for explanation during these thirty years from 76.8 to 31.9 per cent. It is noteworthy, when the appropriate corrections are made for the composition

of the population in regard to age and proportion of Jews, that the diabetes death rate for males actually indicates a decrease since 1900 (Chart IV). For males at least, diabetes in New York City has not been growing more prevalent. In females the figures, corrected as for males, show an elevation of the death rate from

CHART IV.



14.6 to 20.9 per 100,000 between 1900 and 1930, an increase of 43.1 per cent (Chart IV). This points to some distinct difference in the susceptibility to diabetes in the two sexes. This may be partly explained, as previously mentioned, by the growing participation of women in industrial affairs and their subscribing to life

insurance, both of which entail physical examinations. Other factors affecting the two sexes differently will be taken up subsequently.

While these statistical facts lessen the significance which should be attached to the rise in the registered mortality of diabetes, they in no way lessen the great importance of diabetes as a health problem.

The use of insulin has effected great changes in the clinical course of diabetes. According to Dublin's statistics (data of Dr. E. P. Joslin analyzed by the Metropolitan Life Insurance Company) there is a drop from 1900 to 1930 of about 50 per cent in the diabetes deaths due to coma. There is a rise of about 35 per cent in those attributed to cardiovascular conditions, renal disease and gangrene, and of about 15 per cent in diabetic deaths from all other causes.

It is certain that Joslin's results are probably more favorable than those of any other clinic, but even they do not achieve the ideal of perfect control, that is, the entire elimination of diabetic coma. The carelessness of patients and the disregard of diabetes during surgical and other emergencies are mainly responsible for the persistence of a considerable number of coma deaths. The increasing frequence of arteriosclerosis and its complications in the diabetics who live to grow old, thanks to insulin, is well shown in these figures. In our experience the diabetic who has maintained a sugar-free urine almost constantly will not develop these much-dreaded complications. However, the determination of exactly which factors are concerned in the causation of arterial changes and their sequelæ is one of the most urgent problems in our effort to check diabetes. Only when this subject is completely elucidated will it be possible to state with assurance, what can now be only tentatively claimed, namely, that the complete and constant control of diabetes virtually amounts to a cure, even if the disease itself cannot be eradicated.

Treatment. The principles of the treatment of diabetes are established on as sound a basis as is possible with the present-day knowledge of normal and pathologic carbohydrate metabolism in human beings. The accepted criteria for successful treatment are: the constant maintenance of normal nutrition, blood sugar and plasma cholesterol, and a urine free from sugar in the clinical sense. These are very high standards, for it is debatable whether or not the unwavering adherence to natural levels of blood glucose and cholesterol is very significant. The remedial measures, however, used to achieve these ideal objectives of therapy, leave much to be desired.

Within the short period of one generation clinicians have participated in controveries concerning the exclusive administration to diabetics of diets that were, physiologically speaking, distinctly bizarre. We refer to the starvation and high-fat systems of feeding and to the more recent advocacy of excessively large amounts of starch. While extreme diets of this sort meet certain emergencies,

they cannot be used continuously without grave consequences. The routine food intake of the diabetic must be considered suitable in the measure in which it meets the vital needs and the personal tastes of the patient.

Radical changes in the diet may be required for many reasons, such as excessive loss or gain in weight, variations in the carbohydrate tolerance, shifting in the level of the blood sugar and cholesterol, an aversion to or a strong desire for certain foods, the demands incident to surgical intervention or infectious diseases. Essential alterations in the diet should be made only after thoughtful study; carried out by the patient without the aid of medical advice they entail an unwarranted responsibility. For this, as well as for the other reasons to be mentioned subsequently, more frequent medical counsel and less self-treatment than is advocated in many quarters seem desirable in the routine care of diabetic patients.

Many physicians, nurses and patients are openly scornful of the use of qualitative as opposed to quantitative, *i. e.*, weighed diets. Patients with this point of view can be accommodated without distressing or inconveniencing any one except themselves; but the physicians and nurses who insist on accurately weighed and meticulously calculated diets for all cases may spread discontent, and tend to impose an unnecessary burden on many already afflicted with a permanent handicap. Weighed diets are undoubtedly necessary for the satisfactory control of many cases of diabetes, but eating by grams should be avoided whenever possible, since the attendant ceremony and formality tend to provoke an undue nervous tension. A rational dietary, without sugar or sweets, in which the amounts of food with a high-carbohydrate content are approximated by household measures, may often be advisedly carried out when the patient is using insulin. But again, the responsibility should rest entirely with the physician who should be the arbiter of what is most advantageous in each case.

Finally, as regards the self-regulation of the diabetic patient, this disease when it has once appeared is a lifelong problem and its treatment, if it is allowed to become a fulltime occupation to the patient, tends to prove irksome and to result in nervous strain that affects the carbohydrate tolerance unfavorably. The daily urine analysis of a 24-hour specimen by the patient is not advisable. In the first place, the analysis of several single specimens usually yields more valuable information for the regulation of treatment, since this method of examination will determine in which meal the carbohydrates are in excess, or which dose of insulin is insufficient; in the second place, the collection of a complete 24-hour specimen is usually accomplished only with some discomfort and sacrifice; in the third place, the analysis of the patient's urine by himself or one of his family, is likely to be associated with considerable introspective doubt.

Taking all these facts into consideration, it is suggested that the amount of responsibility for self-examination and treatment should be reviewed for each patient with great care. Some patients are unable to be objective about their condition and are rendered unhappy by self-investigation and regulation, while others are able to examine their urine and conduct their treatment very effectively without detriment to themselves.

The family physician should be the hub of the wheel about which routine management of the diabetic patient centers. Postgraduate medical instruction in the simple, direct, effective treatment of diabetes should be constantly available in every large city and thus make it possible for every practitioner to review the principles and methods of therapy at all times. Every hospital should have its resources so organized that the medical, surgical and nursing staffs, the laboratories and diet kitchen are capable of meeting all diabetic problems and emergencies. The occurrence of coma, of a severe infectious disease or other complication in a diabetic patient may call for almost hourly observation and therapeutic adjustment, and is therefore much more satisfactorily controlled in a properly equipped institution than by a single physician in the patient's home. While the routine treatment of the diabetic should be carried out by the family physician, additional medical advice should be sought by him when the ideal objectives of treatment are not maintained, since a deviation from them for a few years or even a few months will result in irreparable damage.

Etiology. The cause of diabetes must be thoroughly understood if reasonable and effective measures are to be carried out for its prevention and cure. The diagnostic criteria and the causes of diabetes have not been satisfactorily defined and, consequently, not all the steps intended to control this disease can be advocated with complete confidence. The enforcement of guides to health, whose validity is not fully established, may result in harm as well as good. We are convinced that all the factors concerned in the causation of diabetes should be subjected to thorough scrutiny and further study, and that meantime public health education on diabetes be confined to an organized effort for the broadcasting of the known facts in regard to the prevalence of diabetes, and the necessity of the conscientious and continuous enforcement of the principles of treatment.

Definition and Diagnosis. Diabetes mellitus may be defined as a disturbance consequent upon a diminished ability of the body to utilize glucose. This is very brief and simple and certainly correct as far as it goes, but it is open to criticism since it does not include the cause of the disease. The impairment of carbohydrate tolerance is usually attributed to changes in the pancreas. Postmortem examinations often reveal such lesions but there are so many instances in which the pathologist fails to demonstrate adequate abnormality

that some skepticism concerning the validity of the unitarian doctrine of the pancreatic etiology of diabetes is justified. The activities of many glands besides the pancreas, such as the adrenal, the thyroid, the liver, the pituitary and numerous others, some partially explored, others scarcely thought of, play a rôle in the assimilation and the oxidation of glucose. The fact that insulin remedies the situation does not warrant our regarding this as a purely substitutional therapy for pancreatic deficiency because its effects may be in part compensatory for an altered activity of other glands. We must consider, therefore, a diminished tolerance for glucose which, according to some is invariably due to pancreatic disease, but, according to others, to extrapancreatic disturbances as well.

The fact that diabetes is thought of primarily as a disease characterized by an impairment of carbohydrate tolerance is demonstrated by the nature of the only diagnostic measure for diabetes in common use today, known as the sugar, or glucose, or carbohydrate tolerance test. This test concerns itself solely with the ability of the body to utilize carbohydrates. Every case of diabetes exhibits a diminished glucose tolerance, but every instance of diminished glucose tolerance is not a case of diabetes. This shows that while our definition of diabetes is the best possible at the present time, it is not an exact description of the disease "diabetes" since there are no pathognomonic signs by which it can be identified. Improvement of the present-day treatment must be based on a clarification of these questions. The possibility that not one but several different forms of abnormal sugar digestion are included under the name "diabetes" is shown by the great and unexpected variations in its onset and in its clinical course.

Though diabetes cannot be accurately described, a consideration of the influences which favor its development is in order. The definition of diabetes is graphically presented in Chart V.

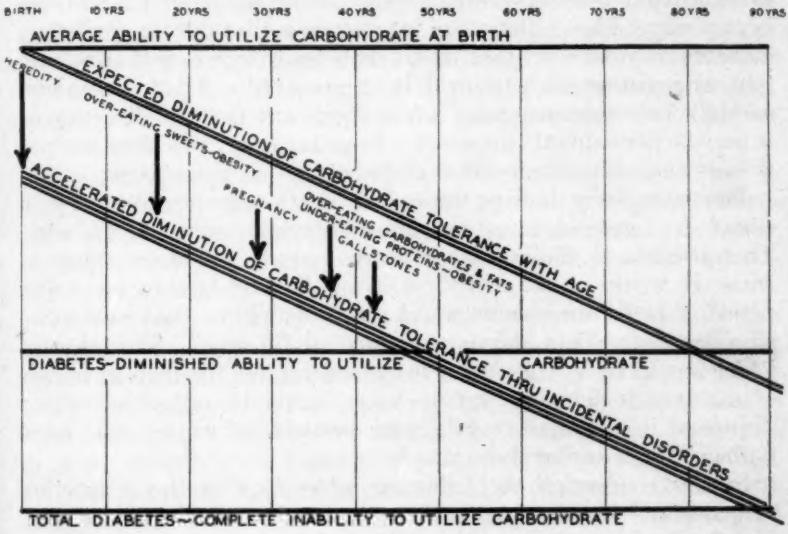
There are three horizontal lines indicating: first, normal carbohydrate tolerance; second, a degree of diminished carbohydrate tolerance at which point diabetes may be thought to begin; and third, the lowest line designed to represent the complete loss of carbohydrate tolerance which, when it exists in human beings, is called total diabetes. On these lines have been plotted the various influences that may in the course of a lifetime be expected to affect the carbohydrate tolerance.

Degenerative Processes, Arteriosclerosis. With advancing years degenerative processes manifest themselves in various organs and tissues in the body, including the glandular structures. This may be caused by the natural wear and tear of the tissues, or may result from arteriosclerosis. It accounts for the diminution of carbohydrate tolerance, that is the mild diabetes, of the aged. The falling line in Chart V, crossing the level of curtailment of carbohydrate tolerance indicative of diabetes at about 80 years of age, is a sug-

gestion of the average course of events in human existence. Some persons will give evidence of diabetes from this cause at 60, 50 or even 40 years of age.

Although this line is a purely arbitrary one, it is undeniable that a constant diminution of carbohydrate tolerance and a tendency to diabetes develops in practically all persons as the result of inevitable degenerative changes. We are accustomed to regard with equanimity rising blood pressure, thinning and graying of the hair, diminution of physical vigor and other marks of deterioration in older individuals, because they are considered to be the unescapable physiologic processes of the passing years. There is every reason to believe that the organs which control the metabolism of glucose

CHART V.—THE INHERENT TENDENCY TO DIABETES IN HUMAN BEINGS AND FACTORS THAT ACCENTUATE IT.



are affected in the same way. Thus the problem of the prevention of diabetes from this cause resolves itself into checking the diseases of old age, which is a general question for solution and is not to be specifically engaged in by those who are interested in perfecting means for the control of diabetes.

Heredity. Heredity is believed to be a factor in about 20 per cent of cases of diabetes. According to some careful investigation, heredity in diabetes appears to follow the Mendelian law. Insulin has enabled youthful diabetic patients to attain maturity and to become fathers and mothers, and has made it possible for the diabetic woman to carry through pregnancies successfully. Because diabetics, since the introduction of insulin, can have children in the

same proportion as normal persons, it is evident that the hereditary factor will result in a rising incidence of diabetes. The influence of an inherited diabetic tendency on the carbohydrate tolerance is indicated in Chart V. The degree and the rapidity of involvement of the carbohydrate tolerance indicated by the lines in Chart V will vary a great deal from case to case, and it must be understood that in its present form this graph expresses only tendencies, and not hard and fast curves of mathematical precision. The solution of controlling heredity as a cause for diabetes is, according to all present-day humanistic principles, not a direct one but a policy of patience that waits for the discovery of a cure for diabetes.

Pregnancy. Pregnancy has a marked influence upon carbohydrate tolerance and diabetes. Renal glycosuria, a permeability of the kidney to glucose below the normal level of blood sugar, is often found in pregnant women. This is a harmless anomaly, not a disturbance of the carbohydrate tolerance, and is not related to diabetes in any way. The consensus of experience is that during pregnancy diabetes may develop, that latent diabetes will be accentuated and that an existing diabetes will be aggravated. After pregnancy, carbohydrate tolerance may return to its antepartum efficiency or it may be permanently impaired. Pregnancy may therefore be considered as an immediate cause of diabetes in some instances.

Pregnancy may damage the carbohydrate tolerance but not to a sufficient degree to cause the immediate appearance of diabetes. The progressive diminution of carbohydrate tolerance expected with age would consequently reach the diabetic level at an earlier period of life in the woman who has borne children than in the one who has not. This idea is expressed in Chart V. This theory, which would be a large factor in accounting for the high incidence of diabetes in females over 45 years, could be either proved or disproved if comparative data were available of women who have borne children and of those who have not.

In this connection the following table showing the proportion of males and females among the diabetes deaths of single persons and those who were married or widowed is of interest.

TABLE 1.—DIABETES—DEATHS AND DEATH RATE IN OLDER ADULTS—NEW YORK CITY, 1931 AND 1932—BY CIVIL CONDITION AND SEX.

	Single.		Married and widowed.	
	M.	F.	M.	F.
Deaths in persons aged 45 years and over	126	106	1,095	2,392
Population in 1930, persons aged 45 years and over	82,494	82,450	644,285	643,827
Rate per 100,000	152.7	128.6	169.9	371.5

The marked preponderance of females among the deaths in married or widowed persons, in contrast to the relative proportion of males and females among the unmarried, lends support to the

belief that pregnancy is an important factor in determining the development of diabetes.

The relation of pregnancy to the diabetes problem, therefore, consists in the avoidance of strain or impairment of the carbohydrate tolerance during puerperium and childbirth. How this is to be accomplished is not known and it is a matter for further investigation to determine what can be done.

Gall Stones. Gall stones are often regarded as a cause of diabetes. A stoppage of the common duct by a calculus results in the forcing of bile into the pancreatic tissue and a consequent injury to the islands of Langerhans. In addition, cholecystitis will affect the carbohydrate tolerance adversely, as is the case with any infection, and it will accelerate degenerative processes and arteriosclerosis, thus favoring the development of diabetes. The interrelation between gall stones, diabetes, cholesterol metabolism, obesity and pregnancy is so complicated that it is impossible to explain it satisfactorily, and most phases of this problem are awaiting an intelligent solution. Since gall stones are more common in women of 40 years or over than in men, another factor besides pregnancy is indicated to explain the greater incidence of diabetes in females over 45 years of age.

The management of gall stones and their complications, with a view to effective prevention of damage to the carbohydrate tolerance, has thus far received scant attention and it would be futile to speculate on this matter because there is a lack of precise knowledge of this subject.

Diet—Obesity. Faulty habits of diet have been blamed for the increasing incidence of diabetes. Improper hygiene not only in regard to eating but also in other directions, especially sedentary habits and lack of exercise, has resulted in an increasing occurrence and degree of obesity which, according to the statistical evidence is associated with an excessive mortality rate in cardiac, arterial and renal diseases, in cancer and in diabetes. Overweight conditions should therefore be prevented if possible. Every degenerative disease gives evidence that obesity has a very adverse influence on the life of human beings. The underweight individual apparently has a better chance to live long than the so-called normal or ideal weight person. This really should be thought of as average weight of apparently healthy individuals, which implies something different than the term normal or ideal weight. The weight standards for the best health which are in vogue at present are apparently too high. Obesity evidently accelerates degenerative changes, that is, deterioration of the tissues and arteriosclerosis, which, as previously suggested, is one of the main processes concerned in the impairment of carbohydrate tolerance resulting in diabetes.

Nutrition is the difference between the amount of food consumed and the quantity utilized by physical effort. The storage of fat,

resulting in obesity, because of a lack of balance of these factors is not synonymous with overeating of fats, starches and sugars, though this is often taken for granted. Obesity is a condition that damages the tissues and strains the functioning organs. The first comes about through fatty infiltration of the tissues; the second is the result of the presence of an excess of body bulk which must be kept warm and which must be carried about. The two handicaps call for separate evaluation and different treatment in each individual. There is a distinct hazard for the obese subject if these two elements in the situation are not given individual consideration. Consequently, propaganda that is made concerning the dangers of obesity should be confined to the necessity and the means for the prevention of obesity, and the control of moderate gains in weight. The reduction of weight for the markedly obese individual, on the other hand, should always be carried out under medical supervision and should not be undertaken with the sole guidance of printed leaflets and radio talks.

The overeating of sugars, starches and fats will result in obesity. The high consumption of sugars and starches is often stated to be a cause of diabetes, independently of the effect they exert through the production of obesity. Charts demonstrating the parallelism between sugar consumption and the incidence of diabetes in different countries have been widely circularized. Such parallelism must not at once be interpreted as a relation of cause and effect. Recent studies in normal persons and in diabetic individuals show that the habitual eating of considerable quantities of sugars and starches improves rather than impairs the carbohydrate tolerance, provided glycosuria is not present. The conclusion, therefore, is warranted that the excessive use of starches and sugars favors the occurrence of diabetes indirectly through obesity, but that the consumption of starches and sugars, even in large amounts, is not a cause of diabetes. In fact, the available evidence indicates that it improves the sugar tolerance. Glycosurias, occurring after high-starch diets, point to a previously existing deficiency of carbohydrate tolerance, that is, a tendency to diabetes. According to these facts there is no reason for limiting the consumption of sugars and starches except insofar as these classes of foods will result in obesity.

The influence of obesity in some respects is more complex than it seemed when this subject was first studied. The association of overweight and hypertension has proved much less constant than originally supposed. Recent studies by Tyner[3] show that "prediabetes" is equally associated with obesity and underweight, that the determining factor in the development of "prediabetes" is age, whose peak is reached in the seventh decade. The relation of obesity to diabetes, therefore, appears to be much more subtle than a simple, direct one of cause and effect.

The proportion of proteins, especially meats, in the average diet

is constantly diminishing. This implies that carbohydrates and fats replace the proteins and tend to cause obesity. Aside from this aspect, which has already been discussed, there is the danger that a deficient protein ration will result in tissue degeneration. Secondary anemia, edema and nephritis have been produced by such diets. It is very probable that an insufficient supply of animal proteins continued for a long time entails degeneration of various organs and arteriosclerosis, which will impair carbohydrate tolerance and accentuate any diabetic tendencies. An educational campaign for the proper use of animal proteins in the routine diet is urgently necessary.

Internal Secretions. The most significant factor in the control of diabetes lies in the functions of the glands of internal secretions. Except for the use of insulin, which has been discussed, there are no practical aids available for general application at present. Consequently, this important phase of the etiology of diabetes is omitted.

Summary and Conclusions. *Organization of Resources in Medicine.* Problems and questions without end have been touched on in this paper. For the promotion of their solution it is proposed that associations of metabolism clinics be organized in various cities. In New York such an association might well be under the auspices of the Academy of Medicine. The activities of such a section within the Academy should not be confined to diabetes, as there are too many other diseases to warrant the creation of a group solely for the study of diabetes, and by implication to segregate a certain number of physicians and specialists in diabetes. Many of us have believed for some time that applied physiology or functional pathology, or pathologic physiology, is as important as anatomic pathology for the understanding of this disease. The medical profession should recognize this by creating a younger brother of the pathologic society.* The phrase, "diseases of metabolism," is in common use but poorly defined; possibly it may be described as that group of disturbances depending upon functional pathology, such as diabetes, hypertension, and so forth. An association of metabolism clinics should bring about a very desirable unification and increased effectiveness of the present sporadic efforts in postgraduate teaching, gathering statistics, carrying out research, improving treatment and initiating preventive measures not only for diabetes mellitus but also for other diseases of equal, if not greater, importance from the point of view of public health.

The Incidence of Diabetes in New York City. Mortality statistics reflect the incidence of diabetes rather than diabetes as a cause of death. The use of insulin has prolonged the life expectancy of diabetic subjects so that, under ideal conditions of treatment, they

* As a pathologist I would like to point out that pathologic societies should, and generally do, regard pathologic physiology as much their field as pathologic anatomy. —EDITOR.

should not succumb to diabetes but to the same diseases as persons not afflicted with diabetes. The method of registering the causes of death will have to be revised if a differentiation shall be made between the incidence and the true mortality rate of diabetes.

An adjustment of the diabetes mortality rate in New York City, according to the aging of the population and the influx of Jews for the past 30 years, shows that during this period the incidence of diabetes in males has not increased at all, while that in females has risen about 40 per cent. The more common and the growing incidence of diabetes in women may be ascribed to two factors: First, the greater participation by women in industrial activities and their more frequent subscription to life insurance, both of which entail physical examinations; second, the injurious effect of pregnancy upon the carbohydrate tolerance has a greater chance to manifest itself as diabetes now, compared to former years, because of our aging population. For these reasons we believe that the rising incidence of diabetes in New York City is more apparent than real.

Our statistics point to the fact that married women are about twice as likely to develop diabetes as married men, while there is no disproportionate ratio between the two sexes in unmarried persons; whether this may be the result of pregnancy directly, or indirectly, through the production of gall stones and obesity, or is due solely to obesity in married women, is an open question, though in our opinion, after a consideration of the available facts, it is pregnancy that impairs the carbohydrate tolerance which manifests itself as diabetes in many women after 45 years; the aging of the population and the use of insulin accentuate this effect of pregnancy on the diabetes mortality rate.

The prolongation of diabetic life through insulin enables men and women who are afflicted with diabetes to become fathers and mothers; consequently the hereditary factor should manifest itself in the future by a rise in the diabetes death rate.

Prevention of Diabetes. It is not feasible to accomplish a great deal in this direction until more complete and reliable information is obtained concerning the onset of diabetes at different ages and in the two sexes, and concerning the etiology of diabetes. The Department of Health can throw light on the problem of diabetes incidence by collecting the results of physical examinations from various sources and possibly by requesting reports of the discovery of diabetes by practitioners. The part played by heredity, menopause, pregnancy, gall stones, glandular activities, nervous disorders and other possible causes of diabetes calls for further investigation before popular statements can be finally and authoritatively made as to the influence these factors exert upon the carbohydrate tolerance in human beings. An educational campaign concerning the eating of meats, fats and carbohydrates, and the dangers of obesity is desirable and warranted by the available facts.

Diabetics Should Not Die of Diabetes. The methods and objectives of diabetes treatment available today are adequate to accomplish this. They are not as universally applied as they should be. In order to bring this about, the treatment should be simplified and be kept free from all unnecessary formalities; more responsibility should be assumed by the physician and less by the patient than is often advocated; opportunities for acquiring the facts concerning the routine management of diabetes should be always available for the practitioner of medicine in the larger cities; every hospital should have its resources so organized that the medical, the surgical and the nursing staffs, the laboratories and the diet kitchens are capable of meeting all diabetic problems and emergencies; every serious illness in a diabetic patient calls for hospitalization and not for home treatment; the physician should not hesitate about insisting on the constant maintenance of the ideal standards of treatment in all his cases, for a deviation from them within a few months or years will result in irreparable damage.

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THE FASTING BLOOD SUGAR IN SCHIZOPHRENIA.

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With the Technical Assistance of Ella K. Ruggles, S.B.*

For the past 5 years the Research Service of this hospital has been conducting an investigation on the schizophrenic psychosis. Among other objects of the research has been that of assembling data for a detailed description of the organic features of a representative group of patients with this psychosis. The details of the project have been previously reported.[1] This paper embodies a discussion of our findings regarding the fasting blood sugar.

The fasting blood-sugar levels in schizophrenia have been determined by a considerable number of investigators, but the results of the various studies have been by no means concordant. In general, as is shown in Table 1 (2 to 22), the results obtained have fallen into three categories. One group of observers has reported

* With the collaboration of the Research Staff of the Worcester State Hospital.

a fairly high incidence of hypoglycemia (below 80 mg. per 100 cc.) but with the majority of the subjects showing normal levels. In the six researches tabulated, 37 of a total of 156 patients (24 per cent) showed hypoglycemia. It is interesting that Smith and Hill[4] found 8 out of 10 patients showed hypoglycemia but after 2 months' thyroid feeding all blood sugars were within normal range.

TABLE 1.—*A.* AUTHORS REPORTING INCIDENCE OF HYPOGLYCEMIA* IN MORE THAN 10 PER CENT OF PATIENTS.

	No. examined.	No. normal.	No. hypoglycemic.	No. hyperglycemic.
2 Genzel	13	10	3	0
3 Looney	40	33	7	0
4 Smith and Hill	10	2	8	0
5 Schrijver	31	22	6	3
6 Kasanin	33	26	5	2
7 Labin†	29	7	8	14
Total	156	100	**37 (24%)**	19

B. AUTHORS REPORTING HYPERGLYCEMIA‡ IN MORE THAN 10 PER CENT OF PATIENTS.

7 Labin†	29	7	8	14
8 Heidema	13	3	0	10
9 Kooy	10	6	0	4
10 Wuth	40	25	0	15
11 Lorenz	52	39	0	13
12 Barrett and Serre	20	15	0	5
13 Mann	23	12	0	11
14 Joó	14	10	0	4
Total	201	117	8	**76 (38%)**

C. AUTHORS REPORTING HIGH INCIDENCE OF NORMAL FINDINGS.

15 Newcomer	6	6	0	0
16 Henry and Mangann	9	9	0	0
17 McCowan and Quastel	29	29	0	0
18 Ström-Olsen	6	6	0	0
19 Weston	30	27	1	2
20 Raphael and Parsons	20	17	2	1
21 Bowman *et al.*	57	51	1	5
22 Sleeper and Hoskins	135	115	12	8
Total	292	**260 (89%)**	16	16
Grand totals	620	470	53	97
(Duplication eliminated)		76%	9%	15%

* Hypoglycemia = 79 mg. per 100 cc. or less.
† Labin appears in two lists.
‡ Hyperglycemia = 121 mg. or more.

A second group of studies made on 201 patients showed an incidence of hyperglycemia in 117 (58 per cent). Labin's[7] 29 patients fall in this group as well as in the preceding.

Finally, records of 8 studies on a total of 292 patients showed

fasting blood-sugar levels within the normal range in all but 32 individuals. In this group, 89 per cent were normal. Newcomer,[15] working with but 6 patients, examined weekly blood samples for from 4 to 7 weeks and found all values to lie within the normal range.

All told, then, we have reports of 620 patients, 76 per cent of whom showed a normal range of blood-sugar findings, 9 per cent showed hypoglycemia, and 15 per cent showed hyperglycemia.

A few other reports are available that do not lend themselves to tabulation. Pighini[23] stated that the blood sugar in schizophrenia is normal, but did not include the data upon which the generalization was based. Drury and Farran-Ridge[24] reported the average values of 18 patients whom they divided into four groups. In females in an acute phase of the psychosis the mean level was 130 mg. and in chronic cases 125 mg. In males the values were 118 and 115 mg., respectively. Reiter,[25] without giving quantitative details, stated that in his experience hyperglycemia occurred no more frequently in schizophrenic than in normal subjects. Tsuchiya[26] in 12 cases found a blood-sugar range from 65 to 100 mg., 3 findings being definitely within the hypoglycemic range. Uyematsu and Soda[27] in 32 patients found a range from 77 to 142 mg., with an average of 99. Their subjects were all catatonics, and the samples were taken 2½ hours after breakfast, hence the results are not strictly comparable with those of the authors previously mentioned.

So far as can be judged by the reports, in none of the studies cited have the results been analyzed statistically with a view to showing any correlations that might exist between the blood-sugar levels and such variables as age, duration of psychosis, period of hospitalization, sex, or type of schizophrenia. Commonly even the emotional state of the patient at the time the sample was taken has not been reported.

Present Study. As previously noted[1] we have had available a group of patients who have served as subjects for an elaborate schedule of studies. Being tested has thus become their daily routine. In such a group, emotional reactions to the testing as such should produce the minimal disturbing effect. On the other hand the individual patient might find the reiterated testing increasingly annoying merely from repetition.

The study herein reported was made on 59 patients. All were males, the average age being 31 years and average period of hospitalization about 5 years. In a measure this represents special selection in that relatively recent cases predominated somewhat to the exclusion of those of long standing, the average period of hospitalization of schizophrenics in Massachusetts being about 11 years. They were further selected in that patients suffering from any organic disease recognizable by careful physical and laboratory

examinations were routinely excluded from the group, as were those over 50 years of age. None had received medication other than occasional cathartics or similar treatment for passing ailments within 3 months of the beginning of the study. A few patients were dismissed from the group after a preliminary period because of intractability. No data from this group are included in the present report. Special care was taken to make sure that we were dealing with cases of schizophrenia in contradistinction to other psychoses with schizoid coloring. The diagnosis in each case represented the unanimous judgment of three psychiatrists as well as two internists and two psychologists who were experienced in dealing with psychotic patients. The same diagnosticians divided the patients into subgroups, but in this latter procedure predominance rather than unanimity of opinion was held to be sufficient.

The composition of the group as to types was as follows: catatonics, 9; hebephrenics, 13; paranoids, 10; simples, 3; mixed, 14; and 10 unclassified.

For purposes of control we made determinations of the fasting sugar levels of 31 normal male subjects living in the hospital. As emphasized by Jenkins,[28] a first consideration of researches of this type is the possibility of systematic laboratory error.

Methods. The Folin-Wu (macro-alkalin-copper tartrate-colorimetric) method was used exclusively. All specimens of blood were obtained from a puncture of the median basilic vein in the cubital space of the forearm. Samples were taken only in the early forenoon after a 15-hour fast. The samples were collected in accordance with the following set schedule:

Collection.	Interval after the first collection.
1	...
2	15 days
3	2 months, 15 days
4	3 months
5	5 months, 15 days
6	6 months

A mixture of potassium oxalate and sodium fluorid was used as an anticoagulant. Sugar standards were accurately checked each time they were renewed and again titrated for deterioration at frequent intervals. All colorimetric readings and the calculations were made by Miss Ruggles under the supervision of Doctor Joseph M. Looney.

Results. The more salient findings of the study are set forth in Table 2. In the control subjects the average fasting blood-sugar level was 95.4 mg. per 100 cc. The lowest value was 80 mg. and the highest 109 mg. That is to say, all findings were within the conventional normal limits. The coefficient of variation was only 6.9 per cent, indicating a rather high degree of homogeneity of the raw data.

Each of the 59 patients was scheduled for 6 sugar determinations, *i. e.*, a total of 354 samples. Satisfactory samples, however, were obtained only in 347 instances. The 7 samples missed were so distributed as to make no significant difference in results. As shown by the table and as illustrated in Fig. 1, the average blood-sugar

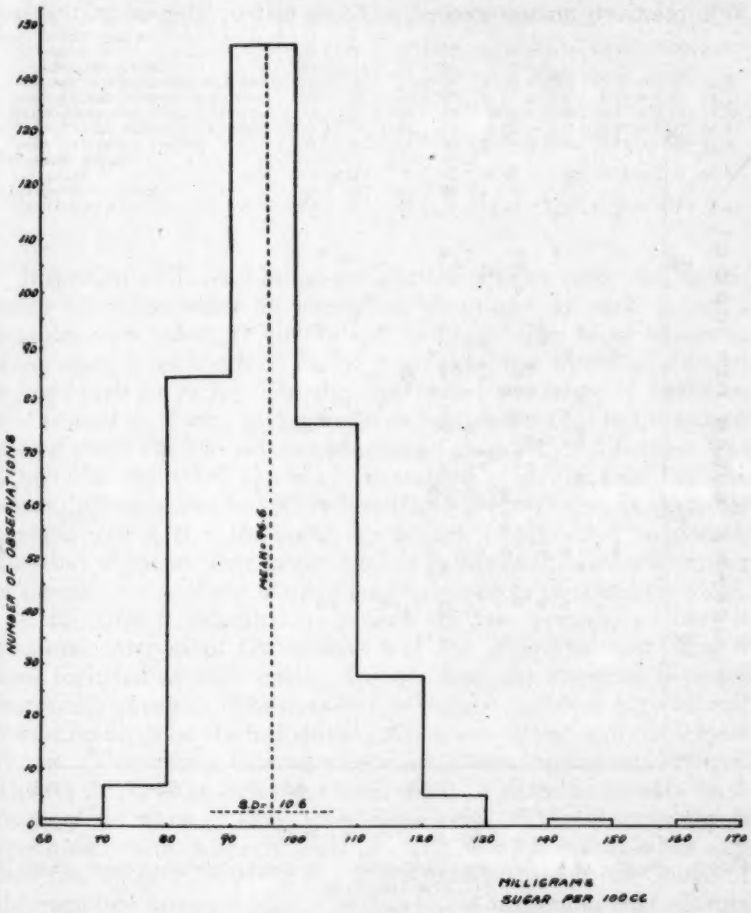

FIG. 1.—Distribution graph showing fasting blood-sugar levels in 347 tests on 59 patients.

level for all determinations was 96.6 mg. per 100 cc. as compared with 95.4 for our normal subjects. The lowest individual mean was 74 mg. and the highest 163 mg. Only 8 of the readings fell below 80 mg., *i. e.*, in the hypoglycemic range, and the same number above 120 mg., which conventionally marks the upper limit of normality. No individual patient was consistently hypoglycemic or hyper-

glycemic in all tests. Thus, 95 per cent of the total readings fell within the normal range. As shown by the coefficient of variation —11 per cent—the data were significantly less homogeneous than in the case of the normal subjects.

Subdividing the data in accordance with the schedule of collections they fall into three groups. In the first subperiod, the patients were relatively unaccustomed to being tested, whereas in the last

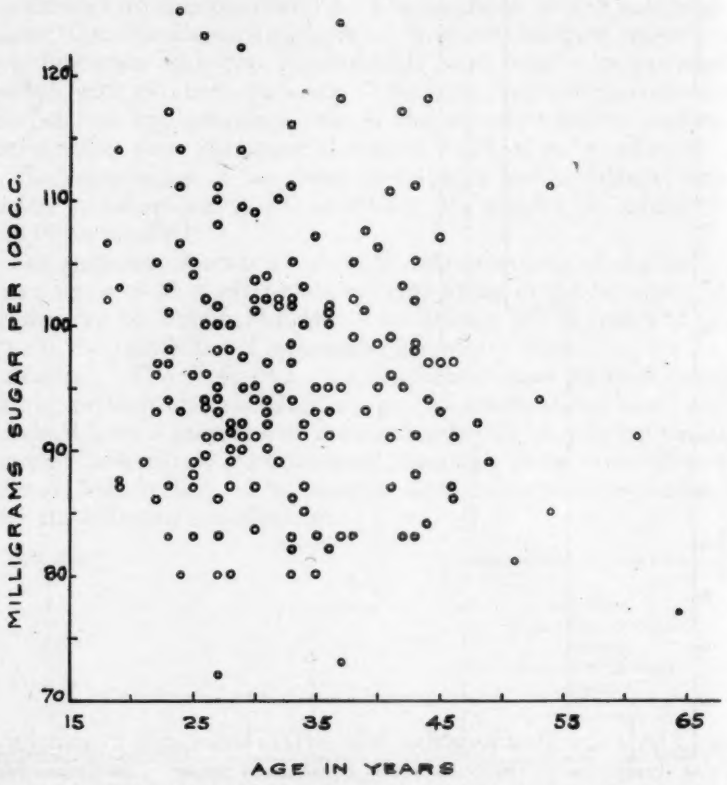

FIG. 2.—Scatter graph showing distribution of fasting blood sugar (mean values) in relation to age.

subperiod testing has become an old story. The suggestion was offered in an earlier paragraph that the average level of fasting blood sugar might be significantly affected by the factor of habituation. This suggestion is borne out by a comparison of results in the three periods. The average in the first instance was 99.3, in the second 96.5, and in the third 93.1 mg. per 100 cc., the individual tendencies falling in with the averages. It is probable, then, that this last value is the most characteristic for schizophrenia, as such.

TABLE 2.—CONSTANTS OF DISTRIBUTIONS PERTAINING TO FASTING BLOOD SUGARS.

	No. readings.	Min.	Max.	Range	Mean.	Standard deviation.	Coefficient of variation.
							Per cent.
Normal controls (mg. sugar)	31	80	109	29	95.40 ± 1.20	6.60 ± 0.85	6.9
Seven months' study							
Age (years)	59	19	45	26	30.98 ± 0.94	10.73 ± 0.67	34.6
Hospitalization (years)	59	0	21	21	5.18 ± 0.47		
Observations on 59 patients (mg. sugar)	347	74	163	89	96.60 ± 0.38	10.60 ± 0.27	11.0
Range of fasting sugars (mg.) 1st period	56	0	38	38	10.57 ± 0.77	8.58 ± 0.55	81.17
Range of fasting sugars (mg.) 2d period	55	0	28	28	9.09 ± 0.62	6.77 ± 0.44	74.48
Range of fasting sugars (mg.) 3d period	59	0	36	36	8.02 ± 0.53	5.99 ± 0.37	44.7
Range of all values, 3 periods	56	10	78	68	25.39 ± 0.96	10.64 ± 0.68	41.9
All research patients							
Age (years)	193	14	61	47	32.47 ± 0.40	8.18 ± 0.28	25.2
Hospitalization (years)	193	0	25	25	4.80 ± 0.22		
Initial fasting sugar values (mg.)	193	72	144	72	96.29 ± 0.52	10.60 ± 0.36	11.0

Inspection of Table 2 brings out another characteristic, the significance of which raises an interesting question. In each period 2 samples were taken at intervals of 15 days. The sugar values in some cases were identical in the 2 samples, but in others differed by as much as 38 mg. In the first period the range of variation was from 0 to 38 mg., with a mean difference of 10.6. In the second period the range was somewhat less and the average difference was 9 mg. In the third the range was about as in the first but the mean difference was further reduced to 8 mg. The most probable explanation of the decreasing variability from period to period, like that of the average sugar level, is habituation, *i. e.*, a lessening of the disturbing factor of emotional reactions to the test procedure.

If the time is extended to include all three periods, we have a maximal interval of $6\frac{1}{2}$ months between individual tests and 6 tests included in each series. In this case, the dispersal becomes materially greater. The smallest difference between highest and lowest readings on the individual patient was 10 mg. and the largest 78 mg. The average difference between extreme values was 25.4 mg. That is to say, the difference was nearly 3 times as great with 6 readings as when 2 only were considered. This observation is presumably only a special case of the general law that when any function, subject to variation, is repeatedly studied, the range of the variation among findings increases to a maximum that mirrors the ultimate potentiality of the factors acting to produce changes.

Correlations. We have material available for a test of the influence of change of clinical state on the sugar level. The psychiatrists had rated all the patients studied into three categories: those whose clinical state improved, those in which it regressed, and those in which it remained essentially unchanged. Table 3 sets forth the data in a contingency table dealing with the blood sugar in these three categories. It is obvious that the changes in the sugar level in relation to changes in the clinical condition show a random dis-

tribution. Hence, no relationship is evident between the depth of the psychosis and the sugar level.

TABLE 3.—RELATION OF CLINICAL CONDITION TO BLOOD SUGAR.

Fasting blood sugar.	Improved.	Regressed.	No change.	Totals.
Higher	1	1	8	10
Lower	4	3	25	32
No change	6	4	11	21
Totals	11	8	44	63

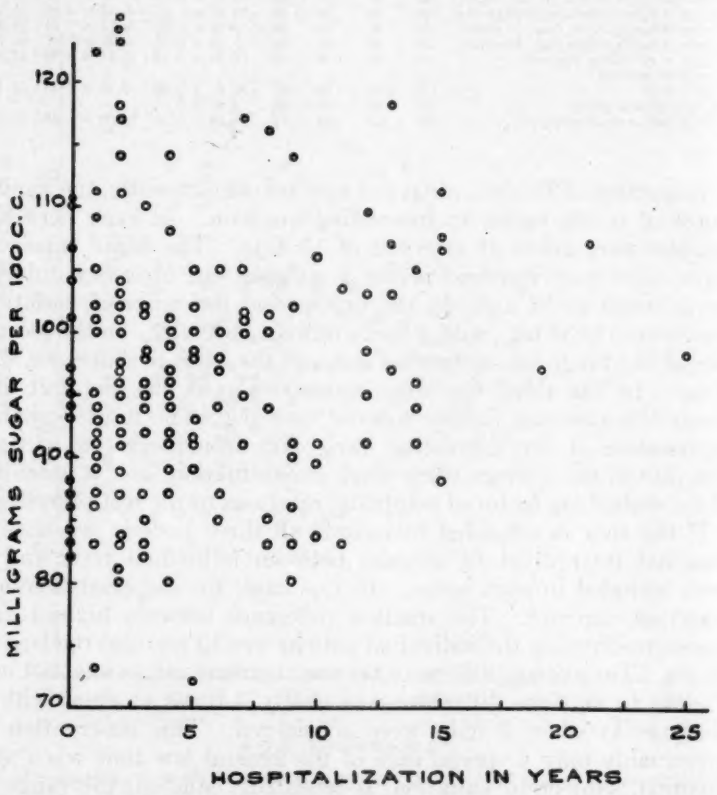

FIG. 3.—Scatter graph showing distribution of fasting blood sugar (mean values) in relation to period of hospitalization.

Since the patients studied by Sleeper and Hoskins[22] were also male schizophrenics and since the methods used in their study were identical with those used in the present study, the two groups of data can be combined for purposes of statistical analysis. The first reading on each patient was utilized for this purpose. In the combined series we then had a total of 193 patients in whom the average age and average hospitalization period were not significantly

different from those making up our "Seven Months' Series." In the larger series, the average fasting blood-sugar level was 96.3 mg. and the standard deviation 10.6, values almost identical with those of the smaller group.

Effects of Age. Kooy[9] as well as Raphael and Parsons[20] interpreted their data as indicating that the age of schizophrenic patients materially affects the blood-sugar level, the older showing a higher level than the younger. Despite the fact that the age range in our series was greater than in theirs, our results (Fig. 2) showed no correlation whatever.

Hospitalization Period. As Kooy[9] has pointed out, it is reasonable to suppose that the longer a patient remains in an institution the more stabilized become his habits of exercise and diet. Hence, it might be expected that in time the sugar level would become stabilized at a minimal level. As shown in Fig. 3, our results in a larger group than Kooy's again failed to show any correlation between the period of hospitalization and sugar level.

Subtypes of Psychosis. Our "Seven Months'" patients, as previously noted, were divided into subgroups. Table 4 shows the average blood-sugar level for each group. The groups are too small to justify general conclusions but as far as they go they appear to indicate the highest level in the hebephrenics (99.5 mg. per 100 cc.) and the lowest in the catatonics (92.7 mg.), with the other groups falling in between.

TABLE 4.—RELATION OF TYPE OF PSYCHOSIS TO BLOOD SUGAR.

No. of patients.	Type.	Mean blood sugar.
9	Catatonic	92.7
13	Hebephrenic	99.5
10	Paranoid	96.3
3	Simple	95.8
14	Mixed	94.9
10	Unclassified	97.9

Summary. A study is presented of the fasting blood-sugar levels as disclosed by 6 samples taken at standard intervals from 59 male schizophrenic patients over a period of 6½ months.

In 95 per cent of 347 determinations the values lay between the conventional limits of normality, namely, 80 and 120 mg. per 100 cc. The average value was 96.6 as compared with an average of 95.4 mg. in 31 normal control subjects studied by the same technique. Eight readings were obtained in the hypoglycemic and 8 in the hyperglycemic ranges.

The variation among the schizophrenics was higher than that in the controls, as was shown by the coefficients of variation, 11 and 6.9 per cent, respectively.

The samples were collected in pairs at 15-day intervals with intervening periods of 2½ months. There was a consistent drop in

the average blood-sugar level from period to period, the first being 99.3 and the third 93.1 mg. per 100 cc. These findings suggest that habituation with a presumable lessening of emotional reaction to the test played a part in determining the sugar level.

The range of difference in consecutive tests also decreased consistently from one period to another; in the first the average difference was 10.6 and in the last 8 mg. per 100 cc.

No significant correlation could be recognized between the blood-sugar level and the age, period of hospitalization, or severity of the psychosis.

Of the subgroups, the hebephrenics showed the highest average level, namely, 99.7 mg., and the catatonics the lowest, namely, 92.7 mg.

Conclusion. Schizophrenia is characterized by normal fasting blood-sugar levels but the individual variability is somewhat greater than in normal subjects.

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STUDIES OF LIVER FUNCTION IN ADVANCED PULMONARY TUBERCULOSIS.*

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Lesions of the liver are found almost constantly at autopsy in cases of advanced pulmonary tuberculosis.[1] Some of these consist of localized foci of tuberculosis; others show some degeneration, usually fatty or amyloid, but occasionally hyperplastic. Fatty degeneration particularly is considered a frequent and serious complication of tuberculosis.[2]

While these lesions have been widely recognized postmortem, it has not been easy to collect convincing evidence of hepatic insufficiency during life. The relative merits of the various laboratory tests of hepatic function are beyond the scope of this report, but it is well to bear in mind that no such test is widely recognized as detecting small lesions of the liver. The liver is a complicated organ. Its functions are numerous and relatively independent of one another, and the biliary functions may be seriously damaged without disturbing the metabolic functions; even the carbohydrate metabolism may be damaged without interference with the protein and fat metabolism. These considerations, and the large "factor of reserve" associated with the gland, explain to some extent why tests of hepatic function have not met with great clinical success.

Nevertheless the clinical detection of hepatic insufficiency in pulmonary tuberculosis has been attempted. Aubertin,[1] in a large series of cases studied with several liver function tests, found that in the progressively deteriorating cases the bad general condition and the hepatic insufficiency ran a remarkably parallel course.

Leuret and Aubertin[3] studied 100 patients, basing their conclusions as to the presence or absence of hepatic insufficiency on clinical observation (symptoms) and on the laboratory tests of urobilinuria, the reaction of Hay, the elevation of the coefficient of Clogne-Derrien, or a slight glycuronic reaction of camphor. Many of the gastro-intestinal symptoms which were considered by these and other authors to be significant of hepatic insufficiency we now know from the work of Brown and Sampson might just as well have been due to intestinal tuberculosis. The presence of

* This study was aided by a grant from the Trudeau Foundation.

hepatic insufficiency was found to follow closely the course of the disease, and transient insufficiency was often accompanied by extensions of the disease.

The Present Study. Twenty-three patients with advanced tuberculosis (19 with far advanced and 4 with moderately advanced) were selected for studies of hepatic function. Five tests were used, the cinchophen oxidation test, the icterus index, the bromsulphalein test, the Congo red and the galactose test. Most patients received all of these tests; in fact some of them were repeated several times. Rarely were less than the five tests done on an individual patient; when hemolysis or a broken tube spoiled a test we did not urge patients unduly who feared venepuncture.

So that all tests might apply to the same clinical condition of the patient, they were completed on any given patient within a period of 2 weeks. It was only the coöperation of a large number of people which made this possible.*

Congo Red. The procedure used in this test was that described by Strasser[4] and Wallace.[5] A 1 per cent solution of the dye was injected in amounts of 0.25 cc. per kg. of body weight. Blood was withdrawn 4 minutes and 1 hour later. Using the first specimen as a standard, colorimetric comparison of the two samples gives the percentage decrease of dye in the plasma. The normal percentage decrease is 10 to 30 per cent. Many technical difficulties occurred in this work, such as hemolysis. In some cases we had to work with low colorimetric readings, which introduced a factor of error. Altogether we felt that the results were more interesting than satisfactory, and the work is reported only for the negative conclusion possible to draw from it. Seven of 19 patients showed readings above the normal of 30 per cent (from 33 to 51 per cent). Although all of these patients also had abnormal function, as evidenced by one or more other tests, these readings were obtained at a time when our calculated possible error could be as great as ±15 per cent, and we are not inclined to attach much significance to them. In 7 patients in whom technical errors were rigidly excluded, the Congo red test showed no abnormality. We believe that this work shows that amyloidosis demonstrable by the Congo red test could not be proved in this series.

Cinchophen Oxidation Test. Lichtman[6] described a test of hepatic function based on the oxidation of cinchophen. After ingestion of 0.45 gm. of cinchophen the excretion of oxycinchophen in the urine

* We are indebted to Dr. Robert Laidlaw for much of the work done with Congo red and to Mr. Carrol Stauff for the titrations in the galactose test. Dr. J. Woods Price, Medical Director of the Reception Hospital, Saranac Lake, kindly placed a number of patients at our disposal, and we are also grateful to Drs. Edgar Mayer and George Wilson for the use of 1 patient at the Northwoods Sanatorium, Saranac Lake. Mr. Donald Cummings, chemist of the Trudeau Foundation at the Saranac Laboratory, was extremely helpful in technical assistance. We are grateful to Miss Ophelia Sawtell for the coöperation of the nursing staff, and to Miss Virginia Reid for secretarial assistance.

TABLE OF COMPARATIVE LIVER FUNCTION TESTS.

Case No.	Icterus index.	Cinchophen.	Bromsulphalein.	Congo red, % decrease.	Galactose.		Advancement of disease.	Degree of toxemia.	Type of disease.
					Concentration (parts per M.).	Output, gm.			
1 . . .	..	179 mg. 37.3%	5m—45% 30m—No trace	0	2h— 6.32 24h— 2.28	1.25 2.17	Far	0	P
2 . . .	..	13 mg. 2.8%	....	25	2h— 4.85 24h— 1.80	0.46 1.03	Mod.	0	P
3 . . .	..	133 mg. 27.7%	5m—25% 30m—No trace	4	2h— 5.58 24h— 1.87	0.76 1.33	Far	Mod.	E
4 . . .	3.0	205 mg. 42.6%	5m—30% 30m—Trace	..	2h— 1.13 24h— 0.88	0.64 1.06	Far	Mod.	P
5 . . .	3.2	259 mg. 54%	5m—35% 30m—No trace	22	2h— 3.37 24h— 1.18	0.54 1.36	Mod.	0	Pntx
6 . . .	3.6	277 mg. 57.8%	5m—30% 30m—No trace	26	2h— 7.42 24h— 3.43	0.24 0.64	Far	Sl.	Pntx
7 . . .	5.1	124 mg. 25.7%	5m—50% 30m—No trace	51	2h— 1.18 24h— 0.57	0.66 1.54	Far	Sl.	Thpl
8 . . .	6.6	203 mg. 42.3%	5m—40% 30m—Trace	38	2h— 2.08 24h— 1.02	0.29 0.48	Far	0	E
9 . . .	7.0	185 mg. 38%	5m—30% 30m—No trace	43	2h— 4.60 24h— 1.55	0.28 1.42	Far	Mod.	E
10 . . .	7.4	123 mg. 25.6%	5m—35% 30m—No trace	38	2h— 5.07 24h— 3.12	0.32 0.55	Far	0	E
11 . . .	7.4	128 mg. 26.7%	5m—35% 30m—No trace	39	2h— 4.00 24h— 1.18	1.48 2.32	Far	Sl.	E
12 . . .	7.5	128 mg. 26.7%	5m—50% 30m—Trace	23	2h— 5.28 24h— 1.66	0.82 1.58	Far	Sl.	E
13 . . .	7.7	126 mg. 26.6%	5m—45% 30m—Sl. trace	33	2h— 2.91 24h— 2.04	0.56 0.89	Mod.	0	Pntx
14 . . .	8.2	146 mg. 30.3%	5m—45% 30m—No trace	29	2h— 0.98 24h— 0.78	0.38 1.32	Mod.	0	P
15 . . .	8.5	151 mg. 31.5%	5m—30% 30m—No trace	20	2h— 2.56 24h— 1.66	0.26 1.46	Far	Extr.	E
16 . . .	10.0	56 mg. 11.6%	5m—40% 30m—No trace	..	2h—10.92 24h— 1.00	0.58 1.17	Far	Sl.	E
17 . . .	10.2	138 mg. 28.8%	....	34	2h— 2.40 24h— 1.02	0.68 1.75	Far	Mod.	E
18 . . .	11.1	....	5m—25% 30m—No trace	38	2h— 6.25 24h— 3.57	2.26 2.57	Far	Mkd.	E
19 . . .	12.4	92 mg. 19.4%	....	..	2h— 5.31 24h— 1.06	0.69 1.29	Far	Sl.	E
20 . . .	12.7	160 mg. 33.4%	5m—30% 30m—No trace	..	2h—17.50 24h— 2.34	1.78 2.52	Far	Sl.	Pntx
21 . . .	15	160 mg. 33.2%	5m—50% 30m—8%	11	2h—10.30 24h— 2.56	0.53 0.86	Far	Sl.	E
22 . . .	15.0	254 mg. 53%	5m—25% 30m—No trace	12	2h—10.29 24h— 1.39	1.09 1.68	Far	Sl.	P
23 . . .	16.0	47 mg. 9.8%	5m—20% 30m—No trace	20	2h— 1.87 24h— 0.53	0.40 0.93	Far	0	E
Upper normal limits . .	7.0	100	No definite amounts after 30 minutes	30	2h—10	2.00			

E = Exudative. P = Productive. Pntx = Pneumothorax. Thpl = Thoracoplasty.

below 100 mg. has been found in normal subjects, while 100 to 150 mg. signify slight liver function disturbance. Results between 150 and 250 mg. signify moderate liver function disturbance, and results above 250 mg. indicate severe functional disturbance. Using the technique described by him we found that 18 of 22 patients excreted more than 100 mg. Eleven of these patients excreted more than 150 mg., and in 3 the excretion was above 200 mg. This test yielded more positive results than any other single test of hepatic function. It is hoped to examine this test as a possible indicator of the activity of a tuberculous process, comparing it with the criteria of activity now in use at the Trudeau Sanatorium.

Galactose Test. Induced galactosuria has recently been given much consideration as a test for hepatic function.

Olivier, Sliosberg and Desnos[7] investigated liver function by the galactose test in 67 patients. Of 41 progressive patients, 32 (77 per cent) gave a pathologic reaction; of 25 patients that were in good general condition with a slight tendency toward progression, 12 (49 per cent) gave a pathologic reaction. Patients treated with gold salts did not give a pathologic reaction any more frequently than other patients. A point of particular interest was that all patients with gastro-intestinal symptoms gave a pathologic reaction.

In Thiébaut and Dieryck's[2] 11 patients the total elimination was often rather low; four times only did it surpass 3 gm., and in 3 patients it was below 1.5 gm. They believed, however, that such figures were not as important as the high level reached in the first fraction in betraying the inability of the liver to metabolize this amount of galactose. In 4 patients in which autopsy was obtained, histologic examination showed diffuse fatty degeneration, and in 3 of these patients, tuberculous foci. They found the test of prognostic value when repeated in the same patient. They agreed with Aubertin that dysfunction of the liver is frequent in tuberculosis and believe that the galactose test is the easiest and most valuable method of gaining this information.

Method Used. The technique used in our series was feeding 40 gm. of galactose in 200 cc. of water at 8 A.M., the patient having fasted since midnight and having voided at 7.45 A.M. The urine was then collected at 10 A.M., 12 NOON, 6 P.M., and the last specimen at 8 A.M. the following morning. During this time the fluid intake was restricted to 1500 cc. The various urine samples were examined for sugar, and the volume was determined. In accordance with the opinion that the concentration should be considered nearly as important as the total output, we have taken above 10 parts per 1000 for the first 2 hours, and a total output above 2 gm. as a pathologic reading. Among 23 patients, 7 gave pathologic readings.

Bromsulphalein Test. Two milligrams of bromsulphalein per kg. of body weight were injected intravenously. Blood was withdrawn from another vein after 5 minutes and after 30 minutes, and com-

pared with standards containing a known percentage of bromsulphalein. In the 20 patients submitted to the test no pathologic readings were obtained.

Icterus Index. The icterus index was satisfactorily determined in 20 patients after the exclusion of a few with whose sera we had some of the technical difficulties to which this test is subject. Readings of 7 or above were considered abnormal. Seven of these patients gave readings between 7 and 10; 8 gave readings between 10 and 16. One patient with an icterus index of 10 and a positive galactose test, who had far advanced exudative tuberculosis with bilateral cavitation, developed an acute appendicitis. Appendectomy had to be done and, while he stood the operation well, there was considerable postoperative bleeding, so much in fact that he had to be reopened. The surgeon failed to find any gross bleeding vessel and accepted latent jaundice as the probable explanation of the bleeding. There were no clinical signs of hepatic insufficiency.

Discussion. By the use of 5 different liver function tests, it is apparent that liver damage may be demonstrated according to the accepted interpretation of these tests in a high percentage of patients. Not every test was always positive in the same patient and it appears to be necessary to use several tests in order to demonstrate during life the liver damage which we know is so commonly found at autopsy. The bromsulphalein test gave us no assistance whatever. The icterus index was positive in 75 per cent of patients; the cinchophen oxidation test was positive in 81.8 per cent; the Congo red test did not give readings above normal in any of the group of patients in which the technique was most carefully controlled, and such readings as were above normal might possibly have been due to technical errors. The galactose test was positive in 30.4 per cent of patients. Two patients with moderately advanced tuberculosis and extreme prolonged digestive disturbances were included in this series because it has been said that the galactose test is always positive in patients having gastro-intestinal disturbances. These patients had had negative gastro-intestinal Roentgen ray films, also gall bladder studies, and had no intestinal tuberculosis as demonstrable by the technique of Brown and Sampson. Neither of them gave a positive galactose test, but both had a positive cinchophen test and one had an elevated icterus index. Though most of the patients in this series had an exudative type of lesion, we are unable to confirm the opinion that exudative lesions are likely to cause abnormal readings in the Congo red test. In fact we did not observe that exudative lesions even of the more intense type caused any particular test to give pathologic readings. The degree of toxicity of the disease as judged by clinical symptoms, for example, fever, tachycardia, night sweats, loss of weight, did not seem to have any relation to any particular test. It was interesting to observe that 3 patients with tuberculous empyema and

mixed infection of the pleural cavity gave pathologic readings only to the cinchophen test.

At the present time it would be more or less speculative to discuss a possible influence of hepatic insufficiency on such procedures as pneumothorax, gold therapy and thoracoplasty, but the fact that liver damage is demonstrable in such a high percentage of patients would seem to indicate that it should be given some consideration at least in the selection of patients for major operative procedures.

Case Abstracts. CASE 1.—A dentist, aged 46, began to cough and expectorate 8 years ago. He had an hemoptysis. He rested partially at home and returned to full time work in 6 months. Repeated Roentgen ray films showed no extension of the disease. He had a fistula in ano and an hemoptysis 2 years ago and stopped work. He had a moderate amount of dyspnea and gaseous indigestion. Two years ago a phrenectomy was done, about 6 months later he had another hemoptysis and pneumothorax was induced. The cavity was never completely collapsed. He had lost 20 pounds in weight and at the time of the tests was a bed patient, his temperature ranging from 96° to 99° F., his pulse from 56 to 88 and his sputum was Gaffky v.

CASE 2.—An Englishman, aged 54, had influenza in 1918 and a year later, *i. e.*, 13 years ago, a diagnosis of tuberculosis was made, based on positive sputum, cough, expectoration, night sweats, fever and hemoptysis, and he went to Albuquerque for a year. Eight years ago he had a serious relapse, including an attack of intestinal and laryngeal tuberculosis, and was treated at Mt. McGregor. His general condition improved so that his larynx is now healed. At the time of the tests his temperature ranged from 97° to 99° F., his pulse from 64 to 100 and his sputum was positive, Gaffky viii.

CASE 3.—A female, aged 32, developed laryngitis 9 years ago. Two years later this was diagnosed as tuberculous, and pulmonary tuberculosis was discovered. She was then at Trudeau Sanatorium for 3 years, during half of which time she worked. She made a good recovery and regained her voice. She then worked at home for 1½ years, but had a relapse of her pulmonary tuberculosis 2 years ago and rested at home. Six months ago her laryngitis recurred and there was a bilateral extension of the pulmonary tuberculosis. The tests were done just prior to the initiation of bilateral pneumothorax and her temperature ranged from 96.2° to 101.4° F., her pulse ranged from 80 to 108 and her sputum was negative.

CASE 4.—A male, aged 25, developed catarrhal symptoms 22 months ago. He was admitted to Trudeau with involvement of both lungs to the 3d rib and bilateral cavitation. Because of massive hemoptyses pneumothorax was begun on the right to control the bleeding 18 months ago. His temperature then was 103.6° F., and pulse 140, but subsided within 3 weeks. Pneumolysis was done 16 months ago. Following an attack of persistent vomiting during the course of positive pressures, he developed a spontaneous pneumothorax a year ago. Hemopneumothorax followed and the patient was desperately ill and tuberculous empyema followed. Because of extremely toxic symptoms which gomenol failed to control, open drainage was instituted 6 months ago and mixed infection, of course, followed. At the time of the liver function tests the daily maximum temperature was 100° F., and pulse 108.

CASE 5.—A male, aged 23, consulted a doctor 1 year ago because of rattling in the left chest. Diagnosis was established at that time. He never had any toxic symptoms at any time. On admission 11 months ago

his Roentgen rays showed a slight lesion of the right apex, and on the left side infiltration to the 3d rib with cavity 2 cm. in diameter in the apex. Seven months ago he was given pneumothorax treatment because of an increase in the size of his cavity. Although only moderately advanced he was included in this series because of long-standing persistent nausea, anorexia and loss of weight for which no adequate cause could be found. Gastro-intestinal series and gall bladder films were negative. He had no toxic symptoms at the time of the liver function tests.

CASE 6.—A male aged 30, had a hemoptoic onset of his disease 2½ years ago. He was a bed patient until his admission to Trudeau, having had two relapses before admission, the latter of which proved to be spontaneous pneumothorax. The disease was of very light intensity in the right lung, radiating from the root into the deeper portions of the lung. The left side showed cavity formation in addition to the spontaneous pneumothorax. The patient never made any marked improvement but continued greatly underweight with occasional elevations of temperature and pulse. There was tuberculous empyema with mixed infection. At the time of the liver function tests his temperature ranged to 101.3° F. and pulse to 100. He was also having hematuria and acid-fast bacilli were present in the urine.

CASE 7.—A male, aged 25, had a hemoptoic onset of his disease 21 months ago. On his first admission to Trudeau 20 months ago he had elevation of temperature and pulse, and several hemoptyses totaling 38 ounces. His Roentgen ray films showed, on the right, infiltration radiating from the root into the deeper portions of the lung; left, infiltration to the 3d rib. Because of massive hemorrhages he was given pneumothorax on the left almost at once. A rectal abscess developed and healed. Tuberculous empyema developed with temperature to 104° F. and pulse to 140. Seven months ago he had recovered sufficiently to permit of a thoracoplasty and, in spite of postoperative infection, his clinical condition at the time of the liver function tests was fairly good. His temperature reached 99° F. daily, and his pulse 90.

CASE 8.—A female, aged 25, developed pleuritic symptoms 6 years ago. A diagnosis of lobar pneumonia was made. It soon became evident, however, that the disease was tuberculosis and she rested for 1½ years. She returned to work, but 6 months later relapsed. On admission to Trudeau 15 months ago she had fever to 100° F., pulse to 116 and Roentgen ray films showed a small amount of infiltration in the middle third on the right and, on the left, infiltration throughout with cavity formation 5 cm. in diameter in the upper third. She was given pneumothorax at once on the left, but developed a serious extension of the disease in the right base with marked symptoms of toxemia. By means of pneumolysis, the cavity on the left closed and the disease on the right showed progressive healing, so that at the time of the liver function tests the patient was in fair clinical condition, although still confined to bed. Her temperature was frequently elevated to 99.4 and 99.6° F. and her pulse still frequently reached 96.

CASE 9.—A male, aged 44, had been ill for the past 6 years, part of which time he was able to work. His toxic symptoms included intermittent night sweats and loss of weight. During these 6 years his disease showed a progressive increase in both lungs, so that when admitted 2 months ago there was infiltration on the right side with cavity 3 by 3 cm., and infiltration on the left side to the 5th rib with cavity formation in the upper third of various sizes. There was also laryngeal tuberculosis. His maximum temperature was persistently 99.6° F. Pneumothorax was begun on the left 6 weeks ago, with a fairly satisfactory collapse and an improvement on the opposite side, including reduction in the size of the cavity. Slight elevation of temperature to 99.2° F. persisted, however, at the time of the liver function tests.

CASE 10.—A female, aged 21, developed acute symptoms resembling pulmonary abscess 4½ years ago. Diagnosis of tuberculosis established by sputum examination at that time. She was in bed for 7 months and in the following 2 years had two relapses. Pneumothorax treatment was started on the left 22 months ago; 20 months ago she had pneumonia on the right, and 19 months ago developed a pleural effusion on the left. She improved symptomatically following this and was practically without symptoms on admission a month ago, at which time it was decided to do a thoracoplasty on the left because of failure of the pneumothorax to collapse large cavities in the upper lung. She had no toxic symptoms at the time of the liver function tests, which were done just prior to thoracoplasty.

CASE 11.—A female, aged 25, developed dry pleurisy 3 years ago, but made a complete recovery. She developed marked fatigue 18 months ago, followed by hoarseness and, for a period of 2 weeks, complete aphonia. She had chills and fever to 104.6° F., at which time tuberculosis was diagnosed. Pneumothorax was begun on the right before her admission to Trudeau 11 months ago. The left lung at the time of her admission showed infiltration of an exudative character in the lower three-fourths. In spite of this very extensive disease her progress in the sanatorium has been fairly satisfactory as a bed patient. At the time of the liver function tests, her fever rose occasionally to 100° F. but for the most part ranged around 99.2° F., and her pulse rate reached a maximum daily average of 100.

CASE 12.—A male Italian, aged 18, noticed a year ago that he had unusual dyspnea while swimming. A month later he began to cough and expectorate, and tubercle bacilli were found in his sputum. He came to Saranac Lake at that time and pneumothorax was induced soon afterward because of the extent and character of the disease and the presence of active symptoms (night sweats, cough, expectoration, hoarseness and fever). Pneumolysis was necessary to secure an effective collapse and after 5 months his symptoms subsided. At the time of the tests his general condition was good. His sputum was positive, Gaffky vi.

CASE 13.—An American housewife, aged 27, had a pleuritic onset 7 years ago which recurred every winter since then, and was accompanied by cough, fatigue and indigestion. She was never very ill, however, and a diagnosis of tuberculosis was not made until 3 years ago, when a Roentgen ray was taken. She was kept in bed 5 months and then given pneumothorax treatment on the right. A complete collapse was obtained, and 11 months later the patient came to Trudeau without symptoms except for severe chronic indigestion which was of 5 years' duration. The course of her disease in the sanatorium was uneventful except for the persistence of severe indigestion. Gastro-intestinal films were negative. Gall bladder films were negative and intestinal tuberculosis could not be demonstrated according to the technique of Brown and Sampson. She was included in these studies because of the impression that such cases of unexplained, persistent, severe indigestion always give a pathologic result to the galactose test. Her temperature and pulse were normal; she was 12 pounds underweight and her sputum was Gaffky i at the time of the tests.

CASE 14.—An American, aged 20, had bronchopneumonia with pleural effusion 17 months ago. He had fever for 3 weeks with night sweats, cough and expectoration. A diagnosis of tuberculosis was made and he came to Saranac Lake a year ago, and was kept in bed. He improved constantly, gaining 75 pounds, partly with the aid of insulin. Six months ago he was allowed up, but 2 months later he had an influenza-like attack and a Roentgen ray showed that a cavity had reopened. Since that time he has been in bed and improving. His temperature at the time of the tests ranged from 96.6° to 98.8° F., pulse from 60 to 100.

CASE 15.—A male, aged 50, past history includes lues and amputation of a finger for destructive osteomyelitis. His tuberculosis began 2 years

ago with a loss of 32 pounds of weight and occasional night sweats. At that time he had bilateral involvement and ran a high fever for a long time. He came to Saranac Lake 6½ months ago and since that time has had marked gastro-intestinal symptoms and fever to 103° F., night sweats and hemoptyses, which symptoms persisted at the time of the liver function tests. He also had mild tuberculous laryngitis. The liver edge was palpable 2 cm. below the costal margin.

CASE 16.—A male, aged 24, had an insidious onset of his disease 2 years ago. Three months ago he had a cold and pleurisy with fever to 101° F. This was followed by an hemoptysis and fever to 104° F. On admission to Trudeau 6 weeks ago he had fever to 99.4° F., pulse to 120, and had a far advanced lesion on the right side to the 5th rib, with a cavity 2 cm. in diameter, and on the left side a lesion to the 7th rib with a cavity 4 cm. in diameter in the middle third. Comparison with films taken 7 weeks previously showed an extension of the disease in both lungs. Films taken 1 month after admission showed extension of the disease in the right lung. At the time the liver function tests were done he had mild symptoms of toxemia and just after the completion of the test bilateral pneumothorax was instituted.

CASE 17.—A female, aged 23, developed catarrhal symptoms 5 years ago and came to Saranac Lake 4 years ago, at which time she had fever, night sweats, loss of strength and weight and hoarseness. She had been constantly a bed patient, her disease intermittently improving and progressing. She was found to have a hypothyroidism with a basal metabolic rate of −30. At the time the liver function tests were done she was about to undergo oleothorax treatment. She was still a strict bed patient. Her daily maximum temperature was 100° F., her pulse 110 and marked fatigue was present.

CASE 18.—A male, aged 26, was perfectly well until 8 months ago. He then developed catarrhal symptoms and loss of weight. He had fever to 99.4° F. He came to Trudeau 3 months ago with fever at that time to 100.2° F.; white blood cells, 11,300; sedimentation rate, 14. Roentgen rays showed infiltration radiating from the root into the middle third on the right, and on the left infiltration to the 5th rib with a cavity 3 by 4 cm. The lesion was exudative. Pneumothorax was begun at once. Two months ago pneumothorax was begun on the right due to an increase of infiltration with development of cavity. At the time of the liver function tests the patient was quite toxic, his maximum temperature ranging from 99.4° to 103.1° F.

CASE 19.—A female American, aged 31, began to cough and expectorate, and grew hoarse 16 months ago. Tubercle bacilli were found in the sputum 13 months ago; 9 months ago she began to experience fatigue, and for 2 months prior to the tests she had a few night sweats. At the time of the tests her temperature ranged from 97° to 99.2° F., her pulse from 72 to 108. She had laryngeal tuberculosis and her sputum was positive, Gaffky viii.

CASE 20.—A male, aged 23, developed catarrhal symptoms 17 months ago, with some hoarseness, loss of strength and temperature to 102° F. for several days. His Roentgen rays showed a lesion of slight intensity on the right side to the 2d rib and on the left side an exudative lesion throughout the lung. Pneumothorax was begun on the left 7 months ago. Since that time his progress has been slow, but showed consistent improvement. He remained in bed during this time, and at the time when the liver function tests were done his daily maximum temperature averaged 99.2° F., and pulse 110.

CASE 21.—A male, aged 29, had rectal abscess 2½ years ago, and catarrhal symptoms 2 years ago followed by hemoptysis. Roentgen rays showed involvement of both lungs, and he spent 10 weeks in the Catskill Mountains. Five months ago he had another hemoptysis, since which time he has been

in bed. Pneumothorax was started 3½ months ago for control of persistent bleeding. During this time the temperature ranged from 100° to 103° F. He lost 10 pounds in weight and had night sweats. His disease at this time spread to the right lung, so that when admitted to Trudeau 2½ months ago he had far advanced tuberculosis with practically no symptoms. At the time of the liver function tests the patient had lost his toxic symptoms but was still confined to bed.

CASE 22.—An American, aged 34, had an acute pneumonic onset 4½ years ago, at which time he had pleural effusion. He has coughed and expectorated since that time and his fever did not completely subside for 6 months. His sputum was found positive 6 months after the onset. He had one hemoptysis and came to Saranac Lake 3½ years ago. Five months after arrival pneumothorax was begun and continued 21 months. A 75 per cent collapse was obtained which did not, however, close the cavity; fluid developed, and the air pocket was lost. His general condition was unfavorable at the time the tests were done. His temperature ranged from 97° to 99.4° F., his pulse from 68 to 108 and his sputum was positive, Gaffsky vii.

CASE 23.—An Englishman, aged 34, was well until he had an influenza-like attack 6 months ago. He returned to work but never regained his strength, and a morning cough and expectoration persisted. Three months ago he felt feverish and had some night sweats, and consulted his doctor. The diagnosis of tuberculosis was made and the patient was sent to Saranac Lake, where pneumothorax was begun 2 months ago. His condition was good at the time of the tests, temperature ranging from 97° to 99° F., pulse from 68 to 88 and sputum was positive, Gaffky vii.

Conclusions. In a series of 23 patients having advanced pulmonary tuberculosis all but one gave pathologic readings in one or more of a group of 5 tests of hepatic function. Of the tests used, the cinchophen test, the icterus index and the galactose test were the most sensitive in the order named.

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LIVER FUNCTION IN CATARRHAL JAUNDICE.

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THERE are admitted to the medical service of every hospital a number of subjects having a painless type of regurgitational[1] jaundice. This group includes several clinical entities, such as carcinoma of the head of the pancreas, salvarsan hepatitis, and

acute yellow atrophy. There remain a number of subjects having an acute jaundice in whom no etiologic agent can be found, and in whom the jaundice spontaneously subsides. To such cases the term catarrhal jaundice is applied. Eppinger[2] says that "every case of jaundice with a sudden onset lasting 1 to several weeks, giving a favorable prognosis, should be included in the group of 'icterus catarrhalis' providing the diagnosis cholelithiasis can be ruled out." Klemperer, Killian and Heyd[3] followed Eppinger by including in the term "icterus catarrhalis" such diverse conditions as: Icterus due to obstruction of the common bile duct following gastro-intestinal catarrh; icterus due to degeneration and multiple areas of necrosis of the liver, and icterus due to cholangitis. Blumer[4] believes catarrhal jaundice to be the sporadic form of epidemic infectious jaundice, the pathology of which was described by Symmers[5] as consisting of acute necrotic changes of the polygonal liver cells without evidence of cholangitis or biliary obstruction. Symmers noted the similarity of this disease and acute yellow atrophy. It is not surprising, since the clinical term "catarrhal jaundice" is represented at necropsy by diverse pathologic findings, that some investigators, including Eppinger,[2] Blumer,[4] Baehr and Klemperer,[6] Jones and Minot,[7] and Moschcowitz,[8] should consider some cases of catarrhal jaundice as examples of acute yellow atrophy that spontaneously recover.

On reviewing the published results of liver-function tests in cases of catarrhal jaundice, it is obvious that the conditions would vary from catarrhal swelling at the duodenal papillæ to an acute necrosis of the liver cells. The functional conditions vary from a retentional to a regurgitational jaundice; from absent bile in the intestines to an increased amount throughout the disease; from no alteration in liver function, except icterus, to a profound disturbance comparable to that found in acute yellow atrophy. Jones and Minot[7] showed by means of duodenal washings that there was marked diminution of the bile entering the intestinal tract during the first or obstructive phase of the disease. Wallace and Diamond[9] by means of the urobilinogen test demonstrated a phase of the disease that was characterized by little or no bile entering the intestinal tract. Mjassnikow and Tschilipenko,[10] however, consider catarrhal jaundice to be characterized from the very beginning by a high urobilinuria. It is evident that the clinical label of "catarrhal jaundice" is applied to dissimilar pathologic or physiologic disturbances. Its evaluation has been rendered more difficult by the great rarity of opportunities for anatomical study of the tissues involved. This study was made to define the pathologic and physiologic features more accurately and to establish criteria for diagnosis in this group of subjects.

Selection of Cases. The subjects of this investigation were patients on the wards of the Third (New York University) Medical and Psychiatric Divisions of Bellevue Hospital. During the period of this study 81 sub-

jects were discharged with the diagnosis of catarrhal jaundice. Of this group 30 individuals were subjected to an intensive liver-function study. The subjects selected were adults below 40 years of age with no history, clinical signs or serologic evidence of syphilis, no history of alcoholism, or taking of drugs for the relief of arthritic or neurotic pains (due to possibility of cincophen or similar poisoning). The jaundice had been acute in onset, painless in character and of short duration. Complete physical, Roentgen ray, serologic and laboratory studies were made. Subjects who were found, after the completion of our investigations, to have another somatic disease, even if it was thought to be unrelated to jaundice, were excluded from this report as were also all subjects who left the hospital before they were sufficiently recovered to confirm the diagnosis.

As a result of this selection of cases only 19 of the 30 subjects studied form the basis of this paper.

The Liver-function Tests Used. 1. Serum bilirubin was determined qualitatively and quantitatively, using Hall's[11] modification of the van den Bergh technique. The serum bilirubin was judged by the following criteria: 0.5 mg. per cent or less, normal; 0.51 to 2 mg. per cent, latent jaundice; 2.1 mg. per cent or over, clinical jaundice.

2. Daily urobilin determinations were made by the method of Wallace and Diamond[9] on a freshly voided specimen of urine collected at approximately the same time each morning. Recognition of urobilin in dilutions greater than 1 to 20, or its complete absence from the urine, was considered abnormal.

3. A qualitative bilirubin determination was performed using Ehrlich's diazo reaction on the same specimen of urine.

4. The original bromsulphalein method of Rosenthal and White[12] was followed for the dye test. The percentage of dye remaining in the blood stream 30 minutes after intravenous injection of 2 mg. per kilogram body weight was determined. The presence of a measurable amount of the dye (5 per cent) at this time was considered abnormal.

5. The levulose tolerance test was performed as soon as practical after the patient was admitted to the hospital, and repeated again before discharge. Occasionally, intermediate tests were performed, but an interval of 7 days or more was allowed between tests. This period was found by Jolliffe[13] to be of sufficient duration to obviate the first or prior test influencing the succeeding tests, as found by Lennox and Bellinger,[14] if the tests followed each other at short intervals. Prior to the test the patients were fasted for 14 hours and the test carried out as in a previous study.[15] The criterion established by Jolliffe,[13] namely, a rise in blood sugar to or over 125 mg. per cent, following the administration of a weighed amount of levulose by mouth, was considered abnormal.

Results. It was concluded early in this investigation that in a majority of subjects we were studying the same entity through several stages. A uniform pathologic and physiologic picture was presented by 16 of the 19 subjects (Cases 1 to 16), which we will designate the "typical group," while the remaining 3 gave findings at variance with those in this group. It was found convenient at the completion of the study on each subject to designate the day on which the maximum concentration of serum bilirubin was found as the "0" day; prior days were labeled as "−5, −4, −3," etc., and days following 0 day were designated as "+1, +2, +3," etc. A very different pathologic and physiologic picture was observed to precede the 0 day, as compared with the subsequent picture.

TABLE 1.—CONDENSED DATA OF 2 TYPICAL AND 3 ATYPICAL CASES.*

Case No.	Days of jaundice before start of study.	Day.†	Urobilinogen.	Bile in urine.	Qualitative van den Bergh.	Serum bilirubin, mg. per cent.	Bromsulphalein, per cent retention.	Levulose tolerance. Blood sugar, mg. per cent.			
								Fasting.	30 minutes.	60 minutes.	120 minutes.
1	4	−4	0	+	Imm.	8.2	35	98	120	142	190
		−2	0	+	Imm.	9.1	40				
		0	0	+	Imm.	10.1	50				
		+1	1:4	+	Imm.	8.1	30	100	113	130	175
		+2	1:160	+	Imm.	5.0	25				
		+3	1:32	+	Imm.	2.6					
		+4	1:16	+	Imm.	2.1					
		+5	1:4	0	Del.	1.8	10				
		+7	1:2	0	Del.	1.6	0				
		+8	1:4	0	..	..	..	100	116	110	98
2	15	−7	0	+	Imm.	11.1	100	83	100	98	83
		−3	1:2	+	Imm.	12.7	100				
		−2	0	+	Imm.	13.0					
		−1	0	+	Imm.	13.8					
		0	1:30	+	Imm.	14.5	100				
		+1	1:90	+	Imm.	10.0					
		+2	1:60	+	Imm.	8.1	90				
		+4	1:10	+	Imm.	4.1	35				
		+7	1:5	0	Imm.	2.2	10				
		+11	1:8	0	Imm.	1.8	F. T.	86	100	72	68
17	1	−2	1:16	0	Del.	5.6	15	105	256	151	153
		−1	1:16	0	Del.	5.8	15				
		0	1:20	0	Del.	6.0					
		+1	1:50	0							
		+2	1:16	0	Del.	4.0	5				
		+3	1:16	0	Del.	3.0					
		+4	1:10	0	Del.	1.2	0				
		+5	1:8	0	..	..	..	83	97	105	90
18	2	−11	1:4	+	Imm.	3.0	0	83	80	117	80
		−9	1:60	+							
		−8	1:2	+	Imm.	3.3	0				
		−6	1:8	+							
		−2	1:30	+	Imm.	3.2	0				
		−1	1:4	+							
		0	1:2	+	Imm.	3.8	0				
		+1	1:2	+							
		+2	1:10	+	Imm.	3.0	0				
		+3	1:1	+	Imm.	2.6					
		+4	1:1	+	Imm.	2.2					
		+6	1:4	0	Del.	1.8					
19	0	−10	1:8	+	Imm.	2.2					
		−7	1:30	+	Imm.	2.4	0				
		−3	1:16	+							
		−2	1:16	+	Imm.	3.5	0	62	66	80	92
		−1	1:20	+	Imm.	3.6	0				
		0	1:8	+	Imm.	3.7	0				
		+1	1:32	+	Imm.	3.0	0				
		+3	1:40	+	Imm.	2.7					
		+5	1:75	+	Imm.	2.5					
		+7	1:16	+	Imm.	2.3					
		+9	1:25	+							
		+11	1:75	0	Imm.	2.0					
		+12	1:25	0							
		+14	1:2	0	Del.	1.1	0				
		+16	1:4	0	..	..	..	67	77	68	65

* To conserve space only Cases 1 and 2 of the 16 cases in the typical group are tabulated. Only a sufficient number of the daily observations are tabulated to illustrate the trend of the tests.

† The day on which the maximum concentration of serum bilirubin occurred was designated as the 0 day; prior days were labeled as −5, −4, −3, etc., and days following the 0 day were labeled as +1, +2, +3, etc.

Serum Bilirubin. The serum bilirubin, as measured by the quantitative van den Bergh reaction, is tabulated for each individual in the accompanying table. The composite bilirubin curve of the typical group is presented in Fig. 1*a*. In each subject there occurred a progressive rise in serum bilirubin until the maximum, which we have designated as the 0 day, was reached. The duration of the jaundice from time icterus was noted by the patient to the height of the jaundice averaged 11 days and varied from 3 to 24 days. In each subject in the typical group following the 0 day there occurred a precipitous fall in the serum bilirubin for 3 to 5 days. In the composite curve (Fig. 1*a*) the bilirubin fell during a 4-day period from 11.1 to 5.2 mg. per cent, almost a 50 per cent fall. During this period observers, not cognizant of the degree of icterus as measured in the laboratory, at times remarked that the jaundice was increasing and only very occasionally noted a decrease, indicating that marked quantitative changes can occur in the serum bilirubin, particularly toward improvement, before this fact can be noted with any degree of accuracy by the observer at the bedside.

Although the serum bilirubin falls rapidly at first, it is not until the +13 day that the composite curve comes within the range of latent jaundice. In every instance the level of latent jaundice was reached by the +24 day, and in one instance by the +2 day. The average duration of jaundice from onset to latent jaundice was 24 days, varying from 8 days (Case 17) to 49 days (Case 4). In the typical group Case 3 was of the shortest duration, 11 days from onset to latent jaundice. The icterus of the skin does not completely disappear by the time latent jaundice is reached, due possibly to the fact that the skin is so stained by the bile pigment, that days or weeks may be required for the pigment to be carried away by the blood or by the desquamation of the epidermis.

The qualitative van den Bergh reaction in the typical group was always of the immediate direct variety during the height of the disease, and, as a rule, when the serum bilirubin was above 2 mg. per cent. In one exception (Case 11) the reaction became delayed at a level of 2.5 mg. per cent. In Subject 17, one of the atypical group, there was a delayed direct reaction even when the serum bilirubin was 5.6 mg. per cent. This subject had, at no time, an increased fragility of the red blood corpuscles to hypotonic saline, abnormal bleeding or coagulation time, or an increase in reticulated red blood cells. Bile was always absent from the urine. In this connection, when bile was present in the urine, the van den Bergh reaction was always of the immediate direct variety. On the other hand, bile may be absent from the urine and the van den Bergh may be of the immediate direct variety. A possible explanation is that the "renal threshold" for immediate direct reacting bilirubin becomes elevated above the conventional 2 mg. per cent level, if the subjects have a jaundice of longer than average duration.

Bile disappeared in the urine while the serum bilirubin level was between 2.1 and 3 mg. per cent in 4 subjects; between 3.1 and 4 mg. per cent in 4 subjects; and at 5.1 mg. per cent in 1 subject. The duration of the jaundice in this group of 9 subjects was 30 days, while in the remaining subjects of the typical group the average duration was 15 days and the average height of the icterus was

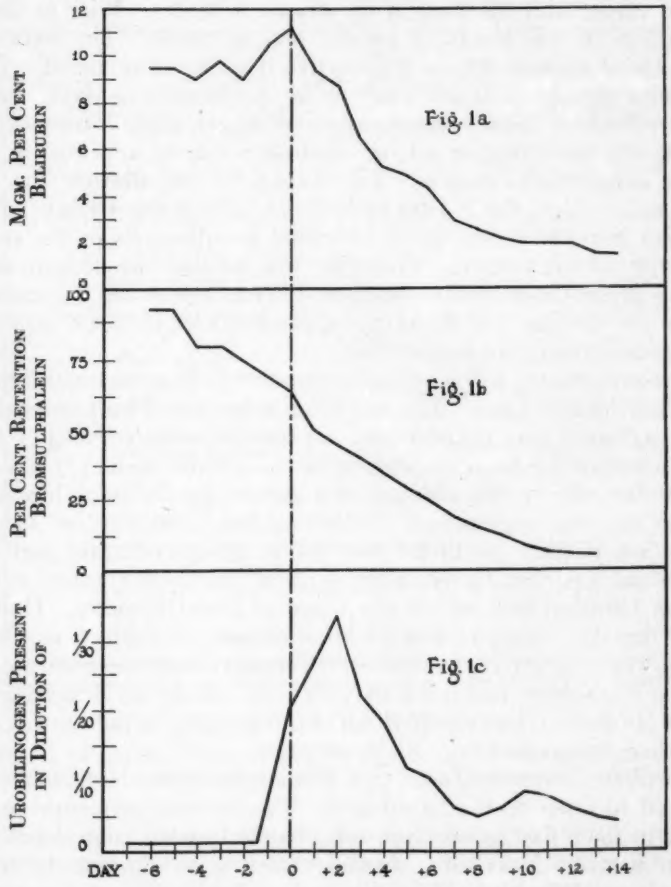

FIG. 1.—The composite serum bilirubin, bromsulphalein, and urobilinogen curves in the typical group.

12.8 mg. per cent on the 0 day as compared to 8.3 mg. per cent in the remaining cases. These facts suggest that a severe icterus, if continued for some time, may cause renal damage.

We have observed that the output of phenolsulphonephthalein in cases suffering from jaundice may be markedly impaired. Bartlett[16] has recently described certain patients who are jaundiced or have

recently been jaundiced and who show a constant inability to excrete phenolsulphonephthalein and to concentrate the urine. He also notes the development of anuria in 2 subjects during jaundice, in whom, 2 weeks prior to onset of the anuria, "the urine was microscopically and chemically normal and the excretion of phenolsulphonephthalein was above 75 per cent."

Urobilin. In the typical group the amount of urobilin in the urine varied with the stage of the disease (Fig. 1*c*). Prior to the 0 day urobilin was absent or present only in traces. The complete absence of urobilin for 10 consecutive days never occurred. Two subjects showed complete absence for 8 consecutive days, otherwise complete absence never occurred longer than 7 consecutive days. On the 0 day or +1 day urobilin suddenly appeared in the urine in increased amounts. The average critical dilution (Fig. 1*c*) rose to 1 to 35 on the +2 day and fell to 1 to 20 on the +4 day. This sudden increase in urobilin in catarrhal jaundice heralds the rapid recovery of the patient. Following the +4 day the urobilin as a rule is present in normal amounts and in no subject was it increased after the +6 day. In the atypical group (Cases 17 to 19) a period of absent urobilin was never noted.

Bromsulphalein. Dye retention paralleled the serum bilirubin in the individual subject. The maximum retention of bromsulphalein occurred on or prior to the 0 day. In the composite curve (Fig. 1*b*), dye retention fell from 90 per cent on the −6 day to 65 per cent on the 0 day, due to the addition of a greater number of subjects as the 0 day was approached. Following the 0 day the fall in dye retention roughly paralleled the fall in serum bilirubin and fell below the 5 per cent level on the +13 day, at the same time as the serum bilirubin well within the range of latent jaundice. On the +14 day dye retention was *nil* in all except one subject, in whom there was a 40 per cent retention. Ten days later the retention of dye in this subject had fallen to 5 per cent. In the atypical group, 2 cases (18 and 19) had no retention of the dye, and in the third (Case 17) there was only a very slight retention.

Levulose Tolerance Test. The levulose tolerance test was performed 40 times on the 19 subjects. The test was performed on or prior to the 0 day on each subject. In the typical group, 14 of the 16 subjects (87.5 per cent) showed a positive tolerance test during this stage of the disease. Subjects 2 and 16 had normal curves. If the severity of the disease can be judged by the intensity of the jaundice, Subject 2 had a severe and Subject 16 a mild attack of catarrhal jaundice. The composite curve of the typical group (Fig. 2*a*) during this stage had a fasting level of 97.8 mg. per cent blood sugar. This compares with a fasting level of 88.7 obtained in this laboratory in 81 tests on 49 normal subjects (Fig. 2*c*).[13] The composite curve rose to 120.8 at the 30-minute period and 132.3 at the 60-minute period, compared to 98.8 and 97.2 at the same

periods in normal subjects. At the 120-minute period the composite blood sugar was 122.4 mg. per cent as compared to 87.6 in normal subjects. The tolerance to levulose was, therefore, in the composite, and in 14 of the 16 individual subjects distinctly abnormal by exceeding the upper limits of a normal response, namely, 125 mg. per cent of blood sugar. In the atypical group, Subject 17 showed an abnormal response, while Subjects 18 and 19 showed normal curves.

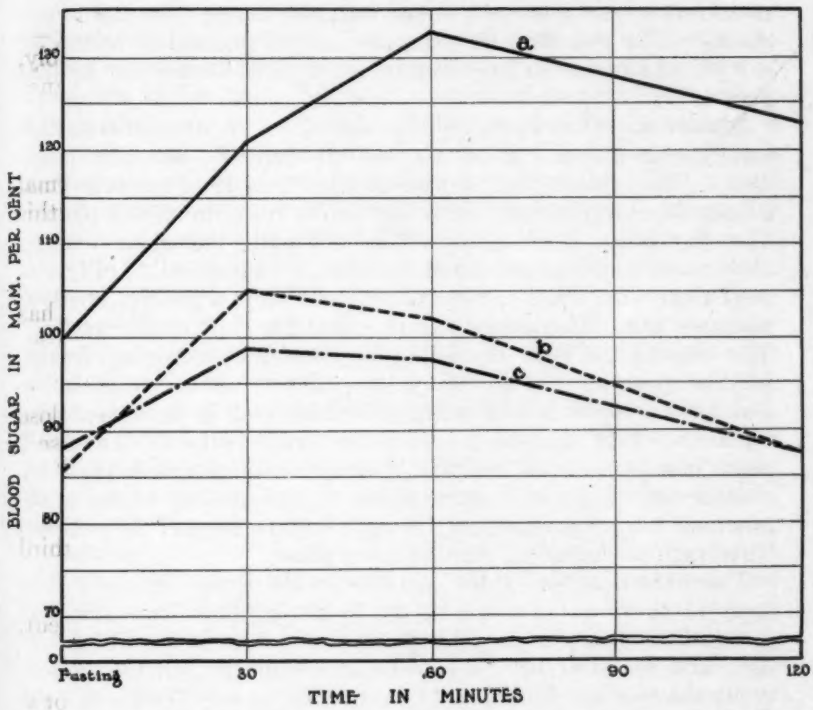

FIG. 2.—Composite levulose tolerance curves. *a*, Typical group prior to the 0 day; *b*, typical group following the 0 day; *c*, average of 81 tests on 49 normal subjects.

Following the 0 day 24 tests were performed on the 19 subjects. Of these tests 3 were positive. Subject 1 on the +1 day showed a positive curve, the blood sugar reaching 175 mg. per cent at the 120-minute period, but on the +8 day the test was normal. Subject 10 on the +3 day had a positive levulose tolerance test in that the blood sugar rose to 135 mg. per cent at the 120-minute interval, but by the +11 day the test was normal. Subject 4 on the +13 day had a slightly abnormal tolerance in that the blood sugar rose to 129 mg. per cent at the 60-minute period. However, on the +24 day the curve was normal. Every subject, therefore, except Case 4, showed a normal levulose tolerance test after the +4 day. The

exception had an unusually severe and prolonged attack of catarrhal jaundice. Every subject eventually showed a normal response to levulose, which fact serves as a control to the tests performed prior to the 0 day. These observations (Fig. 2) indicate that prior to the 0 day subjects of catarrhal jaundice usually, though not invariably, have a diminished tolerance to levulose. This impaired tolerance returns to normal on recovery of the patient. An insufficient number of tests were performed during the first 4 days following the 0 day to draw conclusions on the levulose tolerance during this stage of the disease. The two subjects tested during this period had abnormal curves, which may or may not be the typical finding during this period.

Discussion. Our results indicate that there are at least 3 pathologic groups included under the clinical term of "catarrhal jaundice." The typical group, represented by 16 of 19 of our cases, has a form of regurgitational jaundice[1] which runs through 3 phases. The first phase is characterized by a rapidly increasing icterus, absent or diminished urobilin in the urine, a high retention of bromsulphalein, and usually, though not invariably, a positive levulose tolerance test. This period can be called the "obstructive phase." The second phase lasts for about 4 days, and is characterized by the sudden appearance of urobilin in the urine in normal or excessive amounts, a rapid fall in serum bilirubin, and in bromsulphalen retention. This stage can be called the "critical phase." The third phase begins when the urobilin returns to normal and lasts on an average for 9 days; it is characterized by the gradual return of all functions toward normal and the rapid improvement of the patient. This stage can be called the "recovery phase."

The total duration of the jaundice in the typical group varied from 11 to 49 days, averaging 24 days. In Jones and Minot's[7] series of 23 cases, the jaundice lasted for 14 days or less in 12 subjects and for more than 2 months in 4 subjects. In the typical group the jaundice lasted for 14 days or less in only 3 subjects, and no subject had jaundice for over 2 months. The short duration of the jaundice in this series of cases should be noted in view of the fact that no treatment was directed toward its relief.

Our subjects 18 and 19 were totally dissimilar from the typical group; they have only a mild degree of icterus, a normal levulose tolerance test and an unimpaired ability to excrete bromsulphalein. In no part of their course was there an "obstructive" or "critical phase." This type of jaundice is frequently seen in the Out-Patient Department and is of such a mild character that the patient seldom enters the hospital. One could advance the argument that they are mild cases of the type of jaundice found in the typical group, but the total dissimilarity, especially the absence of an obstructive phase, makes it likely that these 2 cases represent a different entity.

The type of case represented by Subject 17 probably represents a third entity. The jaundice was of the retentional type[1] as evidenced by the absence of bile in the urine and the delayed direct van den Bergh reaction. The levulose tolerance was positive and a slight retention of bromsulphalein was present. The urobilin was normal throughout, except on 1 day. The clinical picture presented by this subject was not unlike that presented by the typical group.

The total dissimilarity of functional tests in the conditions reported in the literature as catarrhal jaundice shows the need for establishing criteria for this diagnosis. Many varieties of acute hepatitis of unknown etiology are clinically similar but unrelated in terms of alteration in function. An acute retentional jaundice with absent bile in the urine and a delayed direct van den Bergh reaction, a regurgitational jaundice characterized by a hyperurobilinuria throughout its course, and a regurgitational jaundice characterized by an obstructive, critical and recovery phase must be dissimilar entities, no matter how similar they may be to the bedside observer. We believe that the entity represented by our typical group, namely, a regurgitational jaundice of acute onset running through three fairly distinctive phases of: (1) obstruction; (2) crisis, and (3) recovery with characteristic laboratory findings in each, deserves the distinction, at present, of a definite label, and that it is to this group alone that the term "catarrhal jaundice" should be applied. It is suggested that the remaining cases be designated as an acute hepatitis of unknown etiology with regurgitational or retentional jaundice, as the case may be, until a larger group has been studied and a better description of them has been made.

Summary. 1. In 19 cases of the type customarily regarded as catarrhal jaundice it has been found that a definite pathologic and physiologic syndrome was present in 16 of the 19. This consists of a regurgitational jaundice which runs through three distinct stages:

(*a*) An "obstructive phase" with an average duration of 11 days in which there is a progressive deepening of the icterus, absent or mere traces of urobilin in the urine, a retention of bromsulphalein paralleling the degree of jaundice and, usually (87.5 per cent), a positive levulose tolerance test.

(*b*) A "critical phase" with an average duration of 4 days in which urobilin suddenly appears in the urine in high normal or definitely elevated amounts, a coincident abrupt fall in serum bilirubin and bromsulphalein retention.

(*c*) A "recovery phase" with an average duration of 9 days during which time the serum bilirubin falls within the level of latent icterus, urobilin is present in the urine in normal amounts and the tolerance to levulose and the retention of bromsulphalein return to normal.

The term "catarrhal jaundice" should be limited to subjects showing this pathologic and physiologic syndrome.

2. The 3 remaining cases were of distinctly different pathologic and physiologic types. It is suggested that these types may be appropriately designated as acute hepatitis of unknown etiology with, as the case may be, retentional or regurgitational jaundice.

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UPPER LOBE BRONCHIECTASIS.*

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In the differential diagnosis of pulmonary tuberculosis considerable significance is ascribed to the site of the lesion. Upper lobe lesions are considered tuberculous unless proven otherwise; lower lobe lesions are considered non-tuberculous unless tubercle bacilli are present in the sputum. Although this generalization holds in the majority of instances in which the diagnosis is open to question, a greater degree of accuracy could be attained if more emphasis were placed on the possible non-tuberculous character of upper lobe disease in which tubercle bacilli are persistently absent from the sputum. Individuals who give a history of cough and expectoration for a number of years without symptoms or signs suggestive of pulmonary neoplasm and who, on physical and Roentgen examination reveal upper lobe involvement, should be suspected of having

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a bronchiectatic condition, provided of course that the sputum does not contain tubercle bacilli.

Bronchiectasis limited dominantly, or entirely, to one or both upper lobes of the lungs is not so rare a condition as might be thought considering the scant mention it receives in the literature. At necropsy on opening the chest, the pleura, over the upper lobes that are the seat of bronchiectatic changes, is almost invariably adherent to the chest wall. The lungs, on cut surface, reveal dilatation of the bronchi leading to one or both upper lobes and, at the periphery of the lung, emphysematous blebs of varying size may be discerned. The former, on superficial examination, may be mistaken for tuberculous cavities; the latter, for spontaneous pneumothoraces. The very large dilatations frequently involve the terminal ramifications of the bronchi near the periphery of the lung. When the walls are unusually thinned out, they themselves may be confused with emphysematous blebs. Macroscopic and microscopic study usually differentiates these conditions. The parenchyma of the affected part of the lung is fibrotic and atelectatic while other parts are distinctly emphysematous.

It must be stated at the outset that bronchiectasis of the upper lobes is, in the majority of instances, the result of a healed tuberculosis although specific elements may be lacking even on microscopic examination of the tissues: a fact true of nearly all long standing tuberculous fibrosis of the lung. To be sure fibrosis, *per se*, even that found in an upper lobe, is not invariably an indication of a preexisting tuberculosis. In some patients, as will be shown later on, the clinical course of the disease, and the presence of fibrocalcific or fibrocaseous nodules in other parts of the lung, suggest that tuberculosis existed previously. In other patients, particularly young persons in whom a history of respiratory infections in childhood is elicited, there is an equal likelihood that the bronchiectatic condition is the result of a non-specific pneumonitis, as is often true in basilar forms of bronchiectasis. In either event, apparently, the process of pulmonary fibrosis and shrinkage produces traction dilatation of the bronchi, the condition being aided by the fixation of the lung to the chest wall. In some lungs, however, the degree of bronchial dilatation is out of proportion to the extent of the peribronchial fibrosis. It is possible that secondary infection of the deeper layers of the bronchial wall may be a factor in the causation of the ectasia. In addition, the constant cough with its attendant rise in intrabronchial pressure very likely plays a significant rôle. Although each of these factors has been considered at one time or another the chief causative agent in the production of bronchiectasis, it is the prevailing authoritative opinion that no single factor explains the condition entirely.

Report of Cases. CASE 1.—J. S., a man, aged 69, gave a history of "pneumonia" 25 years prior to admission. Since then he coughed and

expectorated sputum which was occasionally bloody. He worked all this time. About a year prior to admission he became increasingly more dyspneic, lost weight and his expectoration became more profuse especially in the recumbent position. Physical and Roentgen examinations were characteristic of advanced pulmonary tuberculosis with cavity formation in both upper lobes and emphysema of the lower lobes. There was an associated pulmonary osteoarthropathy of the phalanges of both hands. The sputum was negative for tubercle bacilli on 18 examinations. During his hospital stay of about 2 years his temperature ranged from 97° to 99.5° F. and his chief symptoms were cough, expectoration, increasing dyspnea and cyanosis. He died suddenly October 4, 1930. The lungs, at autopsy, revealed bilateral saccular bronchiectasis in both upper lobes and extensive bronchitis. The right lung, in addition, revealed several large emphysematous blebs on the pleural surface. There was no evidence macroscopically or microscopically of tuberculosis in the lungs or in the other visceral organs. The right auricle and ventricle were hypertrophied and dilated and the coronary arteries sclerotic (Fig. 1).

Case 2.—Y. R., a woman, aged 49, was always in good health until about a year before admission. She complained of asthmatic seizures occurring chiefly at night and characterized by dyspnea and orthopnea lasting several hours. Physical and Roentgen examinations revealed changes that were interpreted as characteristic of fibrotic pulmonary tuberculosis with a cavity in the apex of the right lung. At the hospital, she continued to have paroxysms of dyspnea at irregular intervals which were not relieved by adrenalin. Intramuscular injection of sterile milk as well as injections of parathyroid hormone were of no avail. Examination of the sputum on 6 occasions, including 1 with antiformin, failed to reveal tubercle bacilli. The patient died of right heart failure 5 years after admission. Necropsy revealed bronchiectasis in both upper lobes. Numerous emphysematous blebs were prominent over the upper portions of the lungs, the remainder of the lungs revealing marked emphysema. The heart was hypertrophied and dilated while the visceral organs showed evidences of chronic passive congestion. There was no evidence of pulmonary tuberculosis on gross or microscopic examination of the lungs and other viscera. Microscopic examination revealed marked dilatation of the bronchi with secondary infection, but no tuberculous granulation tissue was found in the sections.

Case 3.—B. O., a woman, aged 72, when admitted gave a history of cough and expectoration of about 20 years' duration, more severe in the preceding 5 years. On many occasions the sputum was streaked with blood. Physical examination revealed changes not unlike those of chronic fibrotic pulmonary tuberculosis of the right upper lobe with cavity formation. The sputum was negative for tubercle bacilli on 4 examinations. The patient remained in the hospital about 14 months when she developed an infection of the lower lip. This was soon complicated by general sepsis which terminated fatally within a few days. Section of the lungs revealed two of the bronchi leading to the right upper lobe to be markedly dilated at the terminal ends. None of the bronchi of the lower lobes or of the left lung was affected. Both lungs, in addition, were the seat of an embolic pneumonia with abscess formation. No tuberculous changes were found in the lungs or in any other organs of the body.

Case 4.—B. R., a man, aged 66, gave a history of cough and expectoration for about 12 years prior to his admission. He was told he had pulmonary tuberculosis 4 years after the onset of his symptoms and he spent some time in health resorts. The physical and Roentgen findings were attributed to chronic fibrocaseous pulmonary tuberculosis with cavity formation involving both lungs. There was evidence of considerable fibrosis and pleuritis. The sputum was negative for tubercle bacilli on 12

occasions, including antiformin examination. He died suddenly 17 months after admission to the hospital. Postmortem examination revealed dense fibrosis and anthracosis in both upper lobes with many bronchiectatic dilatations. In the lower lobes, there were a few small fibrocaseous nodules. Aside from generalized arteriosclerosis which also involved the coronary arteries, there were no striking abnormalities found in the other organs excepting the brain. This organ revealed petechial subarachnoid hemorrhages. Microscopic examination of the lung revealed areas of fibrosis and round-cell infiltrations with several encapsulated foci.

CASE 5.—D. B., a man, aged 55, was admitted to Montefiore Hospital with a history of cough, dating 10 years, productive of thick mucoid expectoration. Lately, the cough had increased in severity and the patient had been growing weaker and had lost weight. Three years prior to his admission to the Tuberculosis Division, he developed cervical lymphadenopathy and splenomegaly. This was diagnosed as chronic lymphatic leukemia and he was treated with radiotherapy. Six months before his admission he had several copious pulmonary hemorrhages. Physical and Roentgen examinations of the chest revealed findings that were interpreted as due to moderately advanced pulmonary tuberculosis involving both upper lobes. The sputum was negative for tubercle bacilli on 4 examinations. He died about a month after admission to the hospital. Necropsy revealed dilatation of the bronchi of both upper lobes and bronchiectatic cavities. Emphysematous blebs were present over both apices. There were several scarred areas but no evidence of active pulmonary tuberculosis was discernible on gross or microscopic examination of any of the viscera. The lower lobes of both lungs were the seat of a terminal coalescing bronchopneumonia. The lymph nodes showed evidences of leukemic changes.

CASE 6.—C. T., a man, aged 51, had had a non-productive cough about 12 years prior to his admission. Later, there was an increase in the expectoration and at one time he spat blood. He also stated that 20 years previously he had "stomach trouble." During his stay at the hospital he had, on occasions, pain in the abdomen that was not related to the intake of food. His pulmonary condition was attributed to chronic pulmonary tuberculosis. The sputum was negative for tubercle bacilli on 4 examinations. He died 2 months after admission. At necropsy, the upper lobes of both lungs were the seat of anthracotic and atelectatic changes, the scarred areas containing numerous small bronchiectatic cavities all lined with thin, smooth, glistening membrane. The bronchi of the other lobes were moderately dilated. No active tuberculous caseation was noted. The stomach contained a carcinoma which had metastasized to the peritoneum and at one point had eroded the wall of the stomach causing a generalized peritonitis. The neoplastic condition was not suspected during life and was accidentally discovered at the autopsy.

CASE 7.—A. C., a woman, aged 52, had "pneumonia with pleurisy" at the age of 34. She dated her present illness, characterized by cough and expectoration, for a period of about 10 years. In the preceding 2 years she had a few copious hemorrhages. She was in several tuberculosis institutions before her admission to the Tuberculosis Division of Montefiore Hospital. Here the physical and Roentgen findings were considered typical of inactive fibrotic pulmonary tuberculosis with cavity formation. A particularly careful study was made of the sputum. On 10 occasions, including several antiformin tests and inoculation of the sputum into 2 guinea pigs, tubercle bacilli could not be demonstrated. In view of our recent experiences, the patient was presented by one of the authors to the staff conference as a case of upper lobe bronchiectasis possibly associated with emphysematous blebs. This diagnosis was confirmed a year later at the necropsy, the patient having died with signs of right heart failure. Over both upper lobes, particularly

the right, there were several large emphysematous blebs. The pulmonary tissue was fibrotic and the seat of many dilated bronchi in both upper lobes. The right ventricle of the heart was hypertrophied and there was congestion of the abdominal viscera. No changes characteristic of tuberculosis were found anywhere in the body, either on gross or microscopic examination of the tissues (Fig. 2).

CASE 8.—W. G., a man, aged 67, was admitted first to the Cancer Division of Montefiore Hospital with a history that about 9 years previously he began to have abdominal colic and vomiting. He was treated in several hospitals, improved and remained well for the following 6 years. Later, these symptoms recurred. The impression of the staff physicians was that the patient had a penetrating gastric ulcer rather than a cancer, although the latter was not wholly excluded. At this time, also, physical and Roentgen examinations revealed a condition that appeared quite characteristic of bilateral pulmonary tuberculosis with cavity formation. The sputum, however, was negative on 2 examinations. The patient improved and was discharged after a stay of 2 months.

Four years later, the patient applied for readmission, this time to the Tuberculosis Division. His history revealed that since discharge he had increasing dyspnea, chest pains, cough, expectoration and weakness. He had few complaints referable to the abdomen. He was examined by both authors in the Tuberculosis Clinic of the hospital and the impression was that the patient was not suffering from active pulmonary tuberculosis but of a fibrotic condition of both upper lobes and bronchiectasis. He was readmitted with the view of having lipiodol studies of the upper lobe bronchi but this was found impracticable. At the hospital, physical and Roentgen examinations, although quite consistent with a diagnosis of advanced pulmonary tuberculosis, were interpreted as due to upper lobe bronchiectasis that was probably associated with emphysematous blebs. The sputum was negative for tubercle bacilli on 6 examinations. Guinea pig inoculations of the sputum gave also negative results. The patient died rather suddenly about 3 weeks after his readmission.

The postmortem examination of the lungs revealed, in brief, the following: The parietal pleura over both upper halves of the lungs was adherent. Section of the right and left lungs revealed essentially a similar picture. The parenchyma in both upper lobes was considerably shrunken and fibrotic and contained numerous bronchiectatic cavities. Aside from some bronchial dilatation in fibrotic upper portions of both lower lobes, the remainder of the lungs did not show bronchiectatic changes. There were no areas of caseation or tubercle formation in the upper lobes but in the lower lobes there were present small caseous nodules, each surrounded by a fibrous capsule. Emphysematous blebs of varying sizes were distributed along the free borders of both lungs. Over the right upper and left lower lobes these blebs were considerably larger, measuring from 2.5 to 3 cm. in diameter. Ten sections of the lung studied by Dr. C. Spark revealed microscopically marked dilatation of the bronchi, pulmonary emphysema with bleb formation and fibrotic tubercles in the lower lobes. A healed ulcer was found in the stomach with resulting hour-glass contraction of the viscus. The other organs showed no significant changes (Figs. 3 and 4).

Synopses of Cases Reported in the Literature. The literature on upper lobe bronchiectasis is rather meager but the few descriptions that are on record make up in interest what they lack in numbers. The following résumé is appended as a source of reference rather than as a complete review of the literature. Although we have been able to find only 16 instances of upper lobe bronchiectasis, there is

FIG. 1.—Case 1, J. S. Numerous, smooth-walled cavities, continuous with bronchi in the upper lobe.

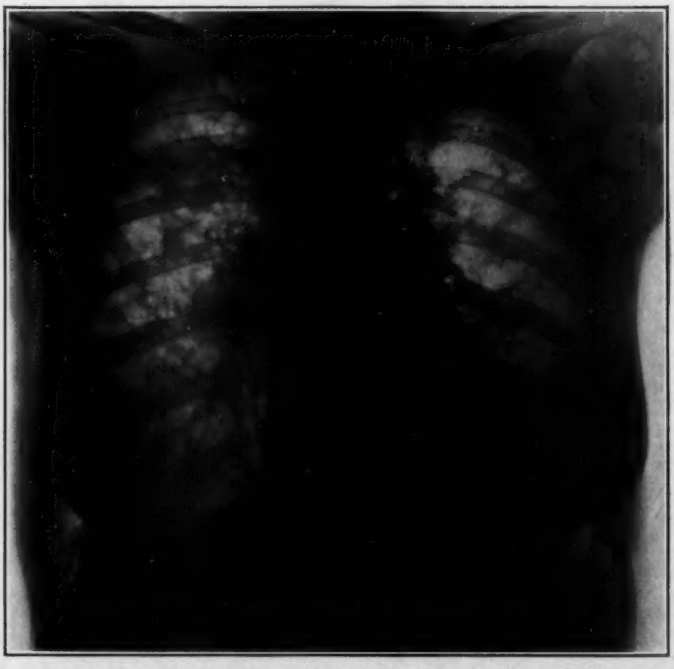

FIG. 2.—Case 7, A. C. Numerous thin-walled rarefactions are visible in the right upper lobe (bronchiectatic cavities and emphysematous blebs). Moderate fibrosis in the remainder of the lung. No pulmonary tuberculosis.

FIG. 3.—Case 8, W. G. Extensive pulmonary fibrosis with areas of rarefaction in both upper lobes (bronchiectasis and emphysematous blebs).

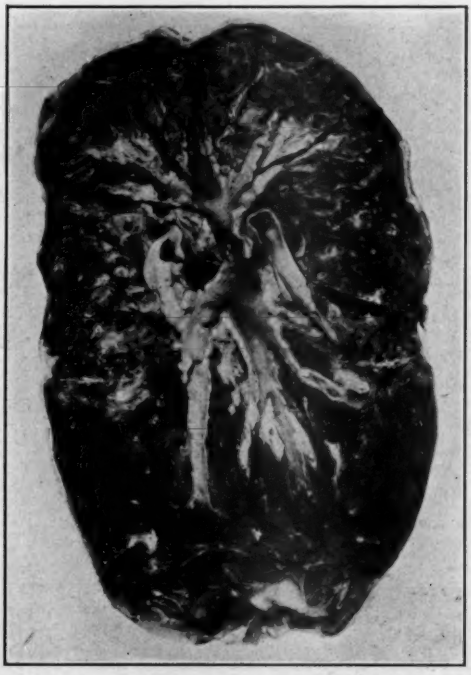

FIG. 4.—Case 8, W. G. Extensive fibrosis and bronchiectatic cavities in the upper lobe. Some bronchial dilatation in fibrotic areas in the upper portion of the lower lobe. Emphysematous blebs (not clearly seen in the photograph) on the pleural surface. Occasional encapsulated tubercle in the lower lobe.

FIG. 5.—Moderate dilatation of the bronchi leading to the right upper lobe (lipiodol injection).

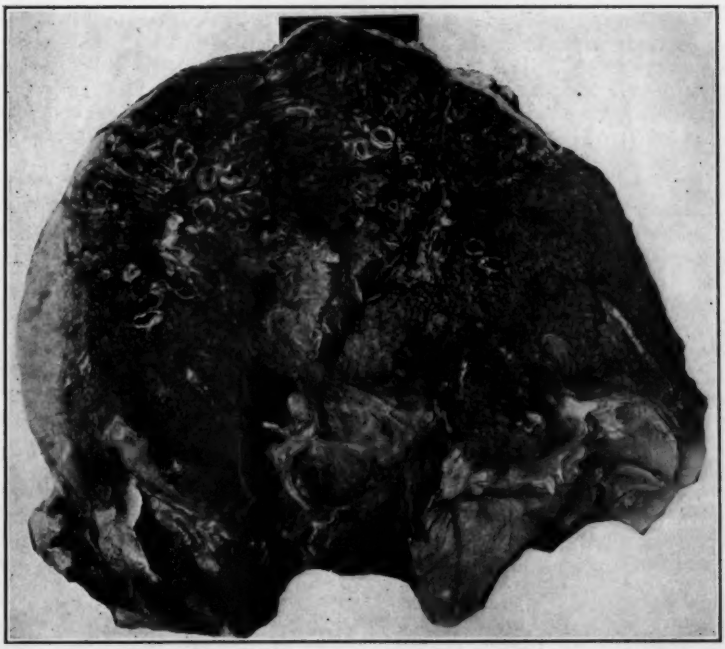

FIG. 6.—J. L. Extensive fibrosis and bronchiectatic cavities in the upper half of the lung and miliary tuberculosis in the lower half.

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no doubt that many more have been described which we have overlooked. Studies on the lobar distribution of bronchiectasis, as observed at autopsy, occasionally include instances in which one or both upper lobes are the only ones involved. But apparently such instances are accidental discoveries, unaccompanied by clinical symptoms of any significance.

CASE 1.—A laborer, aged 59, complained of pulmonary catarrh since infancy, with cough, expectoration but no hemorrhage. Clinically, he was considered tuberculous. Autopsy revealed extensive bronchiectasis of both upper lobes, chiefly the right, with no evidences of tuberculosis (Louis[1]).

CASE 2.—A man, aged 29, was admitted with a history of bronchitis of 2 years' duration. He had seromucous expectoration that was fetid. Examination revealed signs of cavitation in both upper lobes. The condition was diagnosed as upper lobe bronchiectasis. The patient died suddenly and autopsy confirmed the diagnosis (de Cérénville[2]).

CASE 3.—A well nourished woman, aged 25, had a left-sided pneumonia at 11. She had cough, bloody expectoration of nauseous taste and profuse sweating. It was suspected she had dilated bronchi rather than tuberculosis. Autopsy revealed extensive bronchiectasis of both upper lobes, chiefly of the right, with no evidences of tuberculosis (Greenhow[3]).

CASE 4.—A girl, aged 22, gave a history of illness of 3 years' duration following an attack of bronchitis. Because of the convulsive, pertussis-like cough and absence of tubercle bacilli in the sputum, the diagnosis of upper lobe bronchiectasis of the right lung was made. The patient improved with medication (Bruce[4]).

CASE 5.—A man, aged 53, presented symptoms and signs suggestive of pulmonary tuberculosis. From the character of the cough and expectoration and particularly the absence of tubercle bacilli in the sputum, a diagnosis of right upper lobe bronchiectasis was made. Autopsy confirmed the diagnosis (Sottas[5]).

CASE 6.—A woman, aged 58, always in good health, was admitted with a history of illness dating 5 months. She had cough, expectoration and repeated hemorrhages. Tuberculosis was suspected clinically. Autopsy revealed extensive bronchiectasis limited to the right upper lobe. No tuberculosis was seen (Bensaude[6]).

CASE 7.—A man, aged 62, was treated first in the clinic for bronchitis. Later, he developed pulmonary tuberculosis in the left upper lobe and, still later, in the right upper lobe. At this time, tubercle bacilli were found in the sputum. Two years before death he developed tuberculosis of the larynx. Autopsy revealed bilateral upper lobe bronchiectasis in association with healed pulmonary tuberculosis and infiltrative tuberculous laryngitis. No tubercle bacilli were found in the tissues on microscopic examination of the lung (Hauser[7]).

CASE 8.—A cachectic, anemic woman, aged 56, had copious, fetid expectoration that did not contain tubercle bacilli. A clinical diagnosis of unresolved influenzal bronchopneumonia and gangrenous cavity was made. At autopsy there was found bronchiectasis of the left upper lobe which was probably on the basis of a healed pulmonary tuberculosis (Bramwell[8]).

CASE 9.—A 33-year-old epileptic became ill with cough, fever, slight expectoration, dyspnea and loss of weight. No tubercle bacilli were found in the sputum. The patient died of a profuse pulmonary hemorrhage. Autopsy revealed bronchiectasis of the right upper lobe with an aneurysmal dilatation of one of the vessels, the source of the hemorrhage. The diagnosis was not made during life (Bauer[9]).

CASE 10.—A girl, aged 16, suddenly became ill with fever. On the basis of his previous experience, Bauer diagnosed the pathologic changes in the left upper lobe as caused by bronchiectasis. The sputum was negative for tubercle bacilli. The tuberculin test was negative. The patient was treated for a time with pneumothorax and did well (Bauer[10]).

CASE 11.—A girl, aged 13, had been ill several years previously with acute lobar pneumonia of the right upper and left lower lobes, which condition resolved by crisis. The sputum contained pneumococci but no tubercle bacilli. Three years later, she was in good health but examination revealed pathologic changes in the right upper lobe. The sputum was negative. The condition was considered tuberculous. The patient died of an accident. Autopsy revealed bronchiectasis of the right upper lobe with no evidence of tuberculosis (Wingfield[11]).

CASE 12.—A man, aged 62, gave a history of chronic cough for many years. On admission he had cough, expectoration, hemorrhage, dyspnea and loss of weight from 220 to 175 pounds. He was sent to a sanatorium. On his return the impression was that he had a localized non-tuberculous fibrosis of the right upper lobe with some bronchial dilatation. This condition was verified at autopsy. There were no evidences of pulmonary tuberculosis. McCrae and Funk describe 4 other instances of upper lobe bronchiectasis in association with ulcerative pulmonary tuberculosis with cavity formation (McCrae and Funk[12]).

CASES 13 to 15.—Three patients are reported, ranging in age from 22 to 38 years, who had histories of preceding non-specific pneumonitides and whose sputum did not contain tubercle bacilli. Bronchographic examination with lipiodol revealed upper lobe rarefactions which the author ascribed to bronchial dilatations (Knüppel[13]).

CASE 16.—A woman, aged 28, had pneumonia in childhood. She had cough and bloody expectoration. The sputum was negative for tubercle bacilli. Bronchographic examination with lipiodol revealed some 50 cavities with fluid levels in the bronchi of the right upper lobe (Wood[14]).

Diagnosis of Upper Lobe Bronchiectasis. Bronchiectasis should be suspected whenever a patient with a long standing history of cough and expectoration reveals upper lobe lesions in the absence of tubercle bacilli in the sputum on repeated examination. Profuse expectoration, fetid breath, clubbing of the fingers and bouts of fever, classical symptoms in patients with suppurative lower lobe bronchiectasis, are unusual when the upper lobes alone are involved. This is probably due to the better drainage from the latter. Symptomatically, patients with upper lobe bronchiectasis present a picture of chronic fibroid tuberculosis. Increasing dyspnea and weakness, subnormal temperature, blood spitting or frank hemorrhage are characteristic. Tuberculosis of the larynx and intestines occasionally occur in patients with chronic fibroid tuberculosis.[15] They are not present in the bronchiectatic stage of the disease. Right heart failure, coronary occlusion or non-tuberculous bronchopneumonia terminate the disease in the majority of instances.

The physical examination of patients with upper lobe bronchiectasis is of some help in differential diagnosis and probably more so than is the Roentgen film. The reverse is more often the case in active pulmonary tuberculosis. Fishberg[16] has emphasized that in upper lobe bronchiectasis there is occasionally elicited resonance

above the clavicles; a rare occurrence in intensely chronic and long standing pulmonary tuberculosis. Likewise, in upper lobe bronchiectasis signs of apical shrinkage are often lacking; an unusual occurrence in tuberculosis. This may possibly be due to the fact that the largest dilatations of the bronchi are frequently situated subpleurally and the coëxistence of large air-containing emphysematous blebs give a resonant, at times, a tympanitic note on percussion. In some patients, rather than retraction, there is distinct cushion-like bulging of the supraclavicular fossæ. If the pleura is not particularly opaque to the Roentgen ray, one can sometimes discern small circular areas of rarefaction underneath. In this respect a Bucky film is helpful. Occasionally, too, thin-walled emphysematous blebs of varying size can be visualized on a well taken film, but, unless one thinks of upper lobe bronchiectasis the Roentgen configuration can be easily mistaken for tuberculous changes. An important point in differential diagnosis is that in spite of increasing symptoms which the patient may present, comparative films even after a lapse of several years may show surprisingly little change.

Next to the absence of signs of shrinkage of the apex, an important feature of the condition is the absence of tubercle bacilli in the sputum. The presence of active pulmonary tuberculosis makes, of course, any bronchiectatic changes of secondary clinical importance, regardless of the extent of the latter. Although physicians are fully aware of the diagnostic importance of the presence of tubercle bacilli in the sputum, they do not appreciate fully the significance of the absence of tubercle bacilli in the sputum. Peristently "negative" sputum is of greater value in differential diagnosis than is generally appreciated. In a recent study,[17] one of us found that in 99 per cent of patients with advanced pulmonary tuberculosis, tubercle bacilli could be demonstrated in the sputum if at least 3 consecutive examinations were made. In the remaining 1 per cent the patients had chronic or acute miliary tuberculosis, fibrotic acinar nodular tuberculosis, therapeutic or tuberculous pneumothorax or massive pleural effusions. Pinner and Werner,[18] in a study of more than 500 adult patients with active pulmonary tuberculosis, including a considerable number with minimal disease, found tubercle bacilli in over 99 per cent. The diagnostic significance of "negative" sputum cannot be over-emphasized. With the few exceptions noted, the persistent absence of tubercle bacilli in the sputum on repeated examination practically excludes active pulmonary tuberculosis in the adult.

In one instance lipiodol was introduced in a patient in whom we had reason to suspect that a bronchiectatic condition rather than ulcerative tuberculosis existed in the right upper lobe. The patient, a man, aged 48, gave a history of hemorrhage for the preceding 17 years, recurring at irregular intervals, slight cough and expectoration. Since 1914 he had been hospitalized in Montefiore Hospital

and in its Country Sanatorium on 7 previous occasions, as well as in several other institutions. The physical findings revealed no clubbing of the fingers, no retraction of the apices, resonance on percussion, many râles and bronchocavernous breath sounds in both upper lobes, chiefly the right. At one time, in the Country Sanatorium, tubercle bacilli had been present in the sputum, but none was found on this occasion either by direct examination, with antiformin, or by guinea pig inoculation. The results of the lipiodol studies confirmed the clinical impression (Fig. 5). It is very likely that with more frequent use of lipiodol in the differential diagnosis of upper lobe disease, the condition of upper lobe bronchiectasis will be found as a symptomless condition in many more instances than we suspect. But when symptoms are present, bronchographic visualization will not give more information than can be obtained by physical and Roentgen examinations.

Tuberculosis and Apical Bronchiectasis. In a study of the post-mortem findings in approximately 750 patients who died of pulmonary tuberculosis and its complications, the coëxistence of bronchiectasis was recorded in many instances, particularly in elderly individuals with long standing fibrotic disease. Unilateral upper lobe bronchiectasis involved more often the right lung, the site of the older tuberculous process in most patients. However, in the presence of active or even quiescent pulmonary tuberculosis an associated upper lobe bronchiectasis is of relatively minor clinical significance and for this reason such instances are not included in the present study. Our interest centers primarily in such instances of upper lobe bronchiectasis where the condition constitutes the dominant clinical feature of the disease. Recent experiences with 3 patients treated in the Tuberculosis Division of Montefiore Hospital have been particularly instructive, since they demonstrated the evolution of upper lobe bronchiectasis from a previously pathologically active pulmonary tuberculosis.

Case 9.—A man (S. A.), aged 58, was admitted with a history of cough and expectoration of about 25 years' duration. On several occasions, he had blood streaked sputum and quite often paroxysms of dyspnea and cyanosis of the face and hands. The lung findings on physical and Roentgen examinations were characteristic of fibroid pulmonary tuberculosis with cavity formation in the left upper lobe. The sputum was positive. The patient left the hospital but returned on two subsequent occasions, 2 and 3 years later. At the time of the last admission, the physical and Roentgen findings revealed little change from those found previously. The sputum, however, did not contain tubercle bacilli on antiformin examination. The patient died. Autopsy revealed over both upper lobes large emphysematous blebs. In both upper lobes the bronchi were markedly dilated. There were no signs of active pulmonary tuberculosis.

Case 10.—A man (L. P.), aged 49, was an inmate of the Tuberculosis Division for a period of 9 years. Aside from slight cough, expectoration and general debility, he had few symptoms. The physical and Roentgen findings were characteristic of fibrotic pulmonary tuberculosis involving chiefly the upper lobes. During the first 3 years of his stay the sputum contained tubercle bacilli on many occasions. During the remaining 6

years, the sputum was negative to antiformin. The patient died. Postmortem examination revealed grossly a bronchiectatic condition in the left upper lobe and healed fibrotic tuberculosis. Microscopic examination revealed collapse induration of the lungs and anthracosis but no evidence of active pulmonary tuberculosis.

CASE 11.—A man (J. L.), aged 62, was in the Tuberculosis Division for a period of about 2 years. Clinically, he was suspected of having advanced pulmonary tuberculosis with cavity formation, although the sputum was negative for tubercle bacilli on 12 occasions. At necropsy, the patient had a healed fibrotic tuberculosis of the right upper lobe associated with extensive bronchiectasis. The right pleura revealed fibrous pleuritis and heteroplastic bone formation. The left pleura revealed calcified tubercles on the surface. This patient had a terminal miliary pulmonary tuberculosis that did not involve any other organ (Fig. 6).

Although active pulmonary tuberculosis was not demonstrable at necropsy in any of the 3 patients just described, one must presuppose from the presence at one time of tubercle bacilli in the sputum of 2 and the terminal miliary pulmonary tuberculosis in the 3d that a healed pulmonary tuberculosis was the cause of the upper lobe bronchiectasis revealed after necropsy. The end result was the same as in the 8 patients cited previously.

Summary. Bronchiectasis may involve and be confined to one or both upper lobes of the lungs. The clinical and Roentgen findings are in keeping with a diagnosis of chronic, fibro-ulcerative pulmonary tuberculosis with cavity formation. As a result, the patient sooner or later finds himself in an institution for the tuberculous where he is apt to remain for many years to be readmitted after discharge. Although, in the majority of instances the causative factor in the production of these upper lobe bronchiectatic dilatations is a healed pulmonary tuberculosis, it is the bronchiectatic condition that is clinically and morphologically the dominant process. In a lesser number of instances, a practically healed non-tuberculous chronic pneumonitis is the cause of the bronchiectasis.

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THE ASSOCIATION OF BENIGN AND MALIGNANT LESIONS OF THE ESOPHAGUS.*

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The presence of two lesions in the esophagus points to a probable relationship of one to the other. If one is malignant, the association points to the possibility of the benign lesion being, directly or indirectly, the predisposing factor in the development of the malignant lesion. Conversely, however, the possibility of the carcinomatous lesion being the primary lesion, and the benign lesion a direct result of it, must be considered in a certain group of cases.

Fischer, in reviewing the factors which may have a predisposing influence in the production of carcinoma of the esophagus mentioned: (1) The site of scar formation; (2) injury from instrumentation; (3) chronic inflammatory processes, with the development of carcinoma in leukoplakia; (4) irritation by alcoholic beverages, and (5) chronic irritation from some extrinsic pressure as by aneurysm. Since the majority of carcinomas of the esophagus occur at the physiologic narrowings, he believes that pressure plays an important part. Ewing is of the opinion that anomalies of structure of the esophageal mucosa may be predisposing factors in the development of carcinoma but their exact importance has not been determined.

The probable relationship of the anatomic structure of the physiologic narrowings to the production of carcinoma led Benciolini to make a postmortem study of the esophagus of 44 men aged between 45 and 85 years. In 8 of these, he found at the physiologic narrowings, proliferative changes which included: (1) definite thickening of the mucosal epithelium; (2) round-celled infiltration in the submucosa, and (3) a proliferative reaction in the basal layer breaking through and disrupting the basal membrane. He does not call these changes precarcinomatous, but inflammatory reactions which in themselves are of no significance. Since they occur at the usual sites of formation of carcinoma they may be of some importance.

The relationship of cardiospasm to the production of carcinoma falls into the group entitled chronic inflammation of predisposing causes.[9] The common occurrence of the new growth in the dilated portion of the esophagus is noteworthy. Fleiner, in a study of 40

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cases in which dilatation was present, found 3 in which the lesion had developed in the dilated portion of the esophagus. Comparing these to a group of cases of carcinoma of the esophagus without dilatation from cardiospasm, he computed that malignancy was likely to occur 25 times more often in the dilated esophagus. Wohlwill agreed that dilatation of the esophagus from cardiospasm predisposes to the development of carcinoma, but he thought that Fleiner's figures were too high. He reported 2 cases representative of this group; the patients were men aged 64 and 56. Cardiospasm had been present 17 and 15 years, respectively, before carcinoma developed. Wohlwill referred to a definitely neurotic background in the early symptoms of the first case, and added that if there is a functional basis for the production of cardiospasm and if cardiospasm is a predisposing factor in the production of carcinoma, then there is a functional disturbance playing a part in the development of malignant tumor. Moersch, in his report of cardiospasm among infants showed that probably there is no functional element concerned in true cardiospasm. Wohlwill felt that prompt elimination of the stagnation of food in the esophagus in such cases lessens the chance for the development of malignancy. Cade and Morenas, Giardina, and Rebattu and his associates, and others reported similar cases, the carcinoma developing in the dilated portion of the esophagus.

Neumann, in 1861, recorded the first case of carcinoma developing in a cicatrix. Cattell found an epithelioma in a stricture caused by lye in a man aged 66. Schirmer found a carcinoma beginning in an esophageal cicatrix, at necropsy on a man aged 62, whose history had not disclosed any trouble in the esophagus. Magnusson's patient, a man, aged 41, swallowed lye when 18 months old. Symptoms, apparently due to perforation of the esophagus into the right lung, developed 8 months prior to his death. At necropsy, a carcinoma was found between the physiologic narrowings of the esophagus and for this reason Magnusson felt justified in assuming that it originated in the scar tissue, extensive evidence of which was present in the remaining portion of the esophagus.

Fetzer reported the occurrence in a man, aged 54, of a benign stricture due to pleural adhesions causing kinking of the esophagus, and a second stricture caused by carcinoma.

Ewing stated that the physiologic narrowings form the site of diverticula. That these lesions may be associated with carcinoma has been shown. One of us (Vinson) reported 3 such cases. In the first case only was the carcinoma associated with the diverticulum; it was within the sac and extended to the posterior margin of the esophageal opening. In the second case, the carcinoma was in the middle third and the diverticulum was at the juncture of the pharynx and esophagus, whereas in the third case, the carcinoma occurred in the upper third and the diverticulum was slightly above the

cardia. In a case observed by Kaufmann the inner surface of the diverticulum was "lined with a white pultaceous cornified carcinoma," and in another case the lesion occurred at the entrance to the diverticulum. In another of Kaufmann's cases, a small oval isolated tumor was situated on the anterior wall of the esophagus. "The center of the pale gray red carcinoma showed a long depression of slate gray color which diminishing funnel-shaped, ended in an anthracotic chalky bronchial lymph node over the right bronchus."

The invasion of a fibrous polyp in the esophagus by an epithelioma is recorded by Targett. Schirmer observed an ulcerating carcinoma in close proximity to a lipomatous polyp near the cardiac end of the esophagus.

Multiple benign lesions associated with a malignant lesion are rare. Dean and Gregg reported the occurrence of tuberculosis and carcinoma of the esophagus of a patient with syphilis; the dysphagia improved following antisyphilitic treatment. Crile and Dinsmore saw a man, aged 55, who had a diverticulum, cardiospasm and a carcinoma of the esophagus.

Our search of the literature did not reveal any case of hysterical dysphagia in which carcinoma developed in the esophagus, although Cameron has stated that the type of mucous membrane seen in the esophagus in this condition is prone to undergo malignant degeneration. Suzman recently recorded a case in which carcinoma of the tongue and fauces was associated.

The cases presented here represent the association of carcinoma with 3 benign clinical entities in the esophagus: (1) cardiospasm, (2) cicatricial stricture resulting from the ingestion of lye, and (3) hysterical dysphagia.

Case Abstracts. CASE 1.—A man, aged 34, was examined at The Mayo Clinic April 30, 1925. He had had difficulty in swallowing for 8 years, at first mild, with a feeling of obstruction at the cardia on ingesting solid food. Later, the dysphagia became more marked and was especially pronounced when he attempted to swallow cold liquids. Complete closure of the esophagus had occurred on numerous occasions. These periods had lasted from 6 to 8 hours at a time. Occasionally he had regurgitated food after meals, but this had not occurred during the night. Slight pain in the epigastrium was noted at times. Treatment had consisted of the administration of antispasmodic drugs, with questionable benefit. He had lost 58 pounds.

General examination was essentially negative except for the marked emaciation. Roentgenoscopic examination of the esophagus revealed a smooth, obstructing lesion at the cardia with marked dilatation of the esophagus. May 3, 1925, the cardia was dilated with a hydrostatic dilator, and following this treatment, there was complete relief from dysphagia although further roentgenographic study of the esophagus showed that there was slight lagging of the barium meal at the cardia.

During the next year, the patient gained 40 pounds, but returned to the clinic the latter part of June, 1926, because of slight dysphagia. At that time, a No. 45 French sound was passed through the cardia without obstruc-

tion. The patient did not seem to be suffering from sufficient dysphagia to necessitate further hydrostatic dilatation. No further trouble was experienced until December, 1931, when the patient began to notice progressive dysphagia. When he returned for examination March 25, 1932, there had been a loss of strength and 20 pounds weight. Roentgenograms revealed the presence of an irregular filling defect in the lower portion of the esophagus that extended to within 2.5 cm. of the cardia. Esophagoscopy was done, and a large ulcerating lesion, without obstruction, was found on the left posterior wall of the esophagus. This lack of obstruction was due apparently to the fact that the esophagus was dilated as a result of the previous cardiospasm. A section of tissue removed for microscopic study showed it to be papillary squamous-cell epithelioma, graded 2.

The general condition of the patient was good, and it was hoped that because of this and redundant esophageal tissue, the lesion could be removed at operation. However, on exploration, the growth was found to have extended posteriorly, with fixation around the aorta and spine. The condition was considered inoperable, but deep Roentgen therapy was instituted, and at the last report, December 26, 1932, the patient was still living.

This case differs from most of those reported by other investigators, as the region of malignant disease was sufficiently extensive to produce obstruction in the esophagus and permit an antemortem diagnosis.

Case 2.—A woman, aged 38, came to the clinic for examination January 24, 1923. At the age of 18 months she had swallowed a solution of lye, and following this an esophageal stricture had developed. For 6 years, she had experienced more or less trouble in swallowing, but from the age of 8 to 32, the symptoms of obstruction had been minimal. Dilatations were made when she was 15, and following these, there was a pulmonary complication that suggested the presence of an esophagobronchial fistula. Two years before she came to the clinic for treatment, the obstruction had become marked, and she had lost 40 pounds. Dilatations had been carried out with moderate benefit, but after each there would be complete closure of the esophagus for about 12 hours.

Examination revealed a stricture in the esophagus, about 31 cm. from the incisor teeth. Its appearance on roentgenoscopic examination and at esophagoscopy seemed to indicate that the lesion was benign. For 10 weeks, the stenosis was gradually dilated until a No. 40 French sound could be passed without difficulty. The dysphagia became less marked and the patient was permitted to return home. Four weeks following the last dilatation she experienced a sense of strangulation on swallowing liquids and fever began to develop. Examination disclosed a fistula between the esophagus and left bronchus. It was concluded that this was the result of the dilatation of scar tissue which had produced partial healing after perforation that had occurred 23 years before. Gastrostomy was performed May 23, 1923. The patient died September 24, 1924.

At autopsy, it was found that the esophagus was densely scarred and the periesophageal tissues were infiltrated, but the entire process seemed inflammatory. Microscopic section of the tissue revealed that it was a squamous-cell epithelioma.

Numerous cases of this type have come under observation. It is likely that the scar tissue produced in the esophagus by the swallowing of lye is a predisposing factor in the developing of malignant degeneration. However, it is remarkable that, in our experience,

a malignant lesion in the esophagus has not followed a benign stricture from any other cause than lye.

CASE 3.—A woman, aged 39, came to the clinic July 26, 1929. Nine years previously she had noted mild choking sensations, but this had been relieved by tonsillectomy. One year before admission, she began to have trouble in swallowing especially when attempting to eat solid foods. There had been a slight loss in weight, and rather marked anemia had developed.

At examination, the obstruction was noted high in the esophagus. The concentration of hemoglobin was 42 per cent (Dare), and erythrocytes numbered 4,250,000 per c.mm. All the upper teeth were absent, and few remained below. There was a full denture above and a partial plate below. The corners of the lips were cracked and the tongue was smooth. The spleen could not be palpated. Examination of the esophagus revealed nothing abnormal, and following the passage of a No. 41 French olive into the stomach, the patient was relieved completely from dysphagia. She remained well for 2½ years.

In January, 1932, dysphagia returned and was associated with soreness of the throat, but when the patient was again examined in September, 1932, her general condition seemed better than at the time of the first examination. The concentration of hemoglobin was 85 per cent. Examination of the esophagus revealed an ulcerating lesion at the introitus, and tissue removed for microscopic study was reported to be squamous-cell epithelioma, graded 3.

In the observation of patients suffering from carcinoma of the esophagus one is impressed with the long history of dysphagia in a small group of cases. In a few cases, we have felt that functional dysphagia had been present for many years before carcinoma had appeared, and in several cases of definite hysterical dysphagia, malignant degeneration occurred a few years subsequently.

Summary. The literature relating to benign lesions of the esophagus, which seem to increase the predisposition of the esophageal mucosa to the development of carcinoma, is reviewed. Three cases, cardiospasm, stricture caused by lye and hysterical dysphagia, respectively, each associated with the development of carcinoma of the esophagus, are recorded. It is believed that the case of hysterical dysphagia is the first reported in which carcinoma of the esophagus has developed.

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THE DIAGNOSIS OF CARCINOMA OF THE COLON.

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The subject of carcinoma of the large bowel has been receiving much attention in the past few years. The signs and symptoms of this disease, as described in the textbooks, are so numerous as to be confusing. It would seem that any abdominal complaint might indicate new growth. In order to attempt to clarify the subject, or at least to establish the signs and symptoms of chief significance, it was determined to review a typical group of such cases. An analysis has been made of 53 carcinomas of the colon admitted to this Division in the 10-year period, January 1, 1922, to December 31, 1931.

These cases were grouped as follows:

Location.		*Age Incidence.*	
Cecum	7	Under 20	1
Ascending colon	6	20 to 29	2
Hepatic flexure	6	30 to 39	3
Transverse colon	5	40 to 49	9
Splenic flexure	7	50 to 59	14
Descending colon	4	60 to 69	14
Sigmoid colon	18	70 to 79	9
	—	80 on	1
	53		—
			53

Symptoms. The average duration of symptoms on first observation has been found to be 8 months. The usual story was that of an ailment mild at first, gradually becoming more severe, and finally forcing the patient to consult a physician. Frequently the diagnosis failed to be made by several physicians before some careful man

discovered the disease. In such cases the outstanding complaints were abdominal discomfort or pain and weight loss.

1. The abdominal discomfort at first was apt to be vague and diffuse, giving rise later to a dull pain that was not sufficient to interfere with work. The patients frequently believed that an "indigestion" was present, and related a history of use of cathartics and dietary restriction. Later, if the neoplasm involved the right half of the colon, pain was referred to the right lower or upper quadrants, usually the lower. If the left half was involved, the pain was referred to the umbilical region or below, rarely to the left colonic region. A few of our patients had continuous discomfort; the great majority had periodic attacks of pain. As the obstruction increased, attacks of colic became more frequent and pronounced. In the severe attacks of colic, the pain was usually referred to the same site as when the pain was dull. We were unable to elicit any history of abdominal discomfort in 4 cases. Two of these had cancer of the ascending colon, and 2 of the sigmoid colon.

2. Weight loss was the second prominent symptom. At least 10 pounds, and usually more, were lost, while 1 case had lost 80 pounds. Five patients with annular carcinoma of the left colon had no loss of weight.

3. Constipation is regarded as an outstanding feature of carcinoma of the large bowel. It is more pronounced in lesions of the left half than of the right half of the colon. Much to my surprise, *one-third* of the cases observed never complained of constipation. How much this may have been due to the use of mineral oil and other regulators of the bowel, it is difficult to discover. Certainly the wide use of mineral oil has been a large factor in helping to soften feces so that obstipation is less frequently observed. Of the two-thirds that complained of constipation, we noted an almost uniform report that the constipation gradually became more and more severe. Such patients often were bothered by borborygmus, increased flatus, and belching.

4. Diarrhea in growths above the rectum is an almost negligible symptom. The conventional idea is that the typical case reported alternating periods of constipation and diarrhea. We had only 3 such cases.

5. Blood in the stool was not reported for any tumor situated between the cecum and the splenic flexure in cases of cancer. From this point to the rectum there were many reports of blood in the stool. Of the 18 carcinomas of the sigmoid, 7 reported blood. Occult blood was not searched for in a sufficient number of cases to warrant conclusions; I am inclined to believe that a careful search after a sufficient period on a meat-free diet might be helpful in diagnosis.

6. Mucus in the stool was rarely mentioned by the patient, yet in a few cases there was marked evidence of both mucus and blood.

This was likely to be the case in cancers of the lower sigmoid, where the anatomic differentiation between sigmoid and rectum becomes difficult.

7. The tumor mass was felt only once by rectum. This was in a case in which the growth prolapsed from the sigmoid into the rectum. At operation its location was found to be well up in the middle sigmoid. Above the limit of sigmoidoscopic examination palpable abdominal tumor may be found. In 38 cases where the question of a mass was considered in the history, there were 25 in which a tumor could be palpated and 13 in which no tumor could be felt.

8. Secondary anemia was present to a moderate degree in many cases, and to a marked degree in a few. The polypoid types of growth, rather than the annular cancers, seemed to be associated with the more marked secondary anemias. Their surfaces erode more readily and bleed more freely into the intestine.

9. Obstruction may be chronic or acute. The chronic partial obstruction arises from *annular* or *polypoid* growth in the colon. In the *annular* type there develops a submucous growth in which there is much fibrous tissue. Usually there is but little ulceration. In time the lumen becomes narrow because of contracture of the scar tissue. In the *polypoid* type the tumor grows into the lumen from a part of the wall. This form is often accompanied by necrosis of the growth followed by ulceration of the mucous membrane. Obstruction, in its early stage, may give rise to borborygmus and other symptoms of colonic irritability. Of our cases 85 per cent gave indications of some chronic obstruction. The degree of obstructive symptoms is largely influenced by the segment of bowel involved. In the right half of the colon the contents are liquid, and they find but little difficulty in going through a stenosed lumen. In the left half the contents lose their fluid character to become formed, so that much less stenosis is required to cause obstructive symptoms.

Acute obstruction arises when the lumen becomes suddenly occluded or when the tumor causes an intussusception. In the annular growth acute ileus results when the narrow lumen becomes plugged. The polypoid growth causes acute ileus when ulceration, acute inflammation and edema occur.

In our series 1 case of acute obstruction, due to intussusception, occurred in carcinoma of the cecum. Between the cecum and splenic flexure no other case of obstruction occurred. *One-third* of the patients suffering from cancer of the bowel below this point required emergency surgery because of acute obstruction.

Roentgen ray study of the gastro-intestinal tract has become increasingly useful in diagnosis. In the study of tumors of the large bowel one depends on the administration of barium by mouth and by anus. Of the two methods, the barium enema is the more important. The diagnosis of growth in the bowel is dependent on demonstration of infiltration of the gut wall, with narrowing of its lumen.

In early cases, with carcinoma above the rectosigmoid, barium may fill out the lumen above and below the growth in such a manner as to fail to show the lesion. This error may be avoided by taking a sufficient number of films from different angles. But more important still is the necessity for fluoroscopic examination of the barium enema. With this method the barium may be seen to enter and fill out the bowel as it proceeds. One thus has a splendid opportunity to see any defect or deformity in the bowel wall. Of our 40 cases with reported Roentgen ray findings, 31 had positive diagnosis, 4 were questionable, and *5 were reported negative.*

Differential Diagnosis. 1. CHRONIC DIVERTICULITIS. One source of error in Roentgen diagnosis should be emphasized. Such an error occurs when new growth of the colon is diagnosed as chronic diverticulitis. As previously stated, we are dependent on infiltration of the gut wall with narrowing of the lumen for our diagnosis of cancer. In diverticulitis there may occur a single diverticulum, associated with a chronic inflammation, that simulates new growth. In this condition it is practically impossible to make a pre-operative differential diagnosis. At operation, the problem is still great. It has been my fortune to assist at several major operations on the colon where the lesions were thought to be malignant but which subsequently were proven to be the result of inflammation associated with diverticulitis. It is a most difficult problem. Eggers[1] recently has emphasized this fact, again, by reporting 2 cases of diverticulitis that had carcinoma of the bowel associated with them. He does not believe that diverticulitis is a precancerous disease. He reports these cases as showing the presence of cancer in areas in which the Roentgen ray had demonstrated chronic diverticulitis. The clue to the correct diagnosis must be found elsewhere. "So far as can be made out from statistics, bleeding associated with diverticulitis of the colon alone occurs in 5 per cent of these cases. It is evident, therefore, that great care must be taken to avoid overlooking carcinoma of the colon when there has been bleeding and a diagnosis of diverticulitis has been made by Roentgen ray. In my own cases, if I had depended on the Roentgen ray diagnosis of diverticulitis with bleeding, an error would have been made in 75 per cent of the cases, while if operation had been carried out in all cases, the operation would have been an error in but 25 per cent. It is exceedingly dangerous to make a diagnosis of diverticulitis of the colon even with the aid of the Roentgen ray when there is bleeding associated with it."[2]

2. CHRONIC ULCERATIVE COLITIS. In illustration of the diagnostic problem involved in differentiating between this condition and cancer, the following case is cited:

Case Abstract (B30820).—B. A., aged 27, female, 3 years before admission, had a severe attack of abdominal colic. This was relieved by flatus and loose stool, with blood and mucus. Gastro-intestinal series subse-

quently were reported negative. For 2 years the patient enjoyed good health and gained in weight. She then began to have similar attacks although varying in severity. She went to a rectal specialist at that time. He ordered a barium enema and a gastro-intestinal Roentgen ray examination. The report was negative for disease. Symptoms persisted, with freedom from attacks of 1 to 3 months' duration. The later attacks were quite severe, with lower abdominal pain, nausea and vomiting, and no relief afforded by enemas or irrigations. Suddenly some flatus would be expelled, and feces, blood and mucus would follow with relief of symptoms until the next attack. Finally the patient changed doctors and the third Roentgen ray examination demonstrated a growth in the splenic flexure. This diagnosis was confirmed at operation. This patient was interesting because of her age, the duration of symptoms, the complete failure of two Roentgen ray examinations, and the fact that the colon specialist was content to treat her for almost a year as a case of ulcerative colitis.

3. Peritoneal Abscess.

Case 2 (B21404).—S. E., aged 40, female, had been sick for 2 weeks with pain in the left lower quadrant of the abdomen. Examination showed an ill-defined mass in the pelvis, and tenderness in the left vaginal fornix. There had been no constipation and no suggestion of intestinal disease. White blood cells, 11,000 and polymorphonuclears 80 per cent. Operation for drainage of a pelvic abscess revealed carcinoma of the sigmoid with localized perforation.

4. Ovarian Cyst. I have assisted at three gynecologic operations (not reported in this series) at which, the pre-operative diagnosis being left ovarian cyst, carcinomas of the bowel were found. At times it is admittedly difficult to differentiate between these conditions, but the possibility of cancer of the sigmoid must be borne in mind and a more frequent use made of the barium enema with Roentgen ray study to exclude it.

5. Hyperplastic Tuberculosis. Hyperplastic tuberculosis is usually confined to the cecum and ascending colon. It bears a striking resemblance to malignancy in its clinical history and laboratory findings. The patient has abdominal pain, and loss of weight, but as a rule its course is slower and more insidious. A 3-year history of illness is usual in this disease, as compared with our average 8 months in malignancy. Both produce secondary anemia, and both may give constipation and partial obstruction. The average age of incidence is lower in tuberculosis. The Roentgen ray differentiation may be exceedingly difficult. The presence of tuberculosis elsewhere may be helpful to the diagnosis. Even at operation the distinction may be difficult.

6. Granuloma. Granuloma of the cecum is a pathologic entity that is met now and then. Its cause is not well understood, and its differential diagnosis from carcinoma and hyperplastic tuberculosis is quite difficult. At operation one meets thickened gut walls often with narrowing at one area and thickening and dilatation proximal. The mesenteric lymph nodes may or may not be enlarged. In the single case in my personal experience, I performed a resection

under the impression that I was dealing with a tuberculosis of the cecum. Others have performed similar operations mistaking the condition for carcinoma of the cecum.

Summary. 1. Carcinoma of the colon is a disease of middle and late life.

2. Chief symptoms are abdominal discomfort and loss of weight.

3. Partial obstruction with its characteristic symptoms is usually present.

4. Acute ileus is an important symptom in malignancy of the left side of the colon.

5. Roentgen ray examination should be helpful when both films and fluoroscope are used.

6. The disease must be differentiated from: (*a*) chronic diverticulitis; (*b*) chronic ulcerative colitis; (*c*) peritoneal abscess: (*d*) pelvic and ovarian disease; (*e*) hyperplastic tuberculosis; (*f*) granuloma.

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THE CHOLESTEROL CONTENT OF THE PLASMA IN CHRONIC NEPHRITIS AND RETENTION UREMIA.*

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Chauffard, Laroche and Grigaut[1] state that the blood cholesterol in nephritic subjects without uremia is usually high, but with increasing nitrogen retention it tends to fall as if there were an inverse relation between urea and cholesterol. Schmidt[2] shows that hypercholesterolemia frequently occurs in patients with Bright's disease, high blood pressure and related conditions; when there is marked renal insufficiency, the cholesterol content of the blood falls and may even become subnormal; he stresses the prognostic significance of his data. Henes[3] declares that all cases of chronic nephritis terminating fatally in coma show a hypocholesterolemia. Epstein and Rothschild[4] describe the high blood cholesterol of chronic "parenchymatous" nephritis which, they show, falls

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with the onset of uremia. Campbell[5] thinks that the cholesterol values are high in chronic "parenchymatous" nephritis, less so in chronic "interstitial" nephritis, and declares that in the latter condition a fall in the blood cholesterol occurs if uremia begins. Lesné, Zizine and Sylvestre[6] note a hypocholesterolemia in cases of severe acute nephritis. Fleming[7] calls a falling blood cholesterol a poor prognostic sign portending uremia, irrespective of the presence or absence of edema.

In contrast with the literature cited above, Bennett, Davies and Dodds[8] speak of the blood cholesterol being normal usually in nephritic patients where uremic and cardiovascular changes dominate the picture, as compared with the high cholesterol reading in "nephrosis."

Still further contrast is afforded by the analyses of Maxwell,[3] indicating that a persistently elevated plasma cholesterol occurring in patients who had been edema-free for a long period is often associated with the early onset of uremia. Yet (according to Maxwell), the cholesterol is normal or low in uremia.

Material and Methods. In the present paper the data of 24 cases of chronic Bright's disease are submitted. Only the significant results are tabulated but, in all, over 200 simultaneous determinations of the whole blood urea nitrogen and the plasma cholesterol were made. The majority of these cases were studied for 2 or more years, alternately in the wards of the New York Post-Graduate Hospital and in private practice.

Prior to 1928, the whole blood urea nitrogen was determined according to the method of Myers;[10] since then by the gasometric urease method of Van Slyke.[11] The plasma cholesterol was determined chiefly by Sackett's method[12] modified since 1931 by the temperature control procedure used in this laboratory;[13] rarely by the method of Myers and Wardell.[14]

The numerous analyses in the literature on the cholesterol content of the blood indicate that a plasma cholesterol from 160 to 230 mg. per cent may be considered as "normal." We have often observed a plasma cholesterol (in single blood studies) as high as 250 mg. per cent in "normal" fasting subjects (laboratory workers, interns, etc.). For these reasons we have considered a plasma cholesterol below 160 mg. per cent as subnormal (hypocholesterolemia), from 160 to 230 mg. per cent as the average normal range, from 230 to 250 mg. per cent as suggestive of hypercholesterolemia but still within the normal limits, and above 250 mg. per cent as definitely elevated (hypercholesterolemia).

Analysis of Data. Table 1 comprises the data on the simultaneous determinations of the whole blood urea nitrogen and the plasma cholesterol in 9 patients who died in uremic coma. The terminal urea nitrogen is high—over 100 mg. per cent in 8 of the 9 cases. The plasma cholesterol, terminally, is low or average normal (as

low as 83 mg. per cent in Case 3) in all cases except Case 9. In this patient the last cholesterol determination (250 mg. per cent) was made 2 days before death. There is a reasonable likelihood that the cholesterol on the day of death was lower than 250 mg. per cent; for example, we may cite Case 8, in which the cholesterol fell from 217 to 178 mg. per cent in 24 hours before death occurred in uremia.

From a study of Table 1 (and a comparison with Table 3) we observe that the finding of a low plasma cholesterol in a patient with marked nitrogen retention is of more prognostic value as to predicting death in uremia than the level of the blood urea nitrogen. For example, of the patients dying in uremic coma manifesting a low plasma cholesterol, Case 2 had a terminal urea nitrogen of 100 mg. per cent, Case 4, 86 mg., and Case 9, 119 mg. Yet, in Table 3 we have recorded patients with a high plasma cholesterol who did well and were relieved of uremic symptoms although the blood urea nitrogen was as high or higher than the 3 fatal cases cited. Moreover, in any individual case the same fact is often observed. We have seen patients feeling well and going about their work for months with a blood urea nitrogen almost as high as (rarely higher than) that recorded at the time of death. At the time when they were ambulatory the plasma cholesterol was high; terminally the cholesterol was low.

There appears to be no close relation between the height of the plasma cholesterol and the degree of edema manifested by these patients. In Case 1 there was no appreciable difference in the amount of edema when the cholesterol ranged from 477 to 667 mg. per cent on the one hand, as compared to the edema noted when the cholesterol ranged from 200 to 172 mg. per cent, on the other. In Case 9 fluctuations of the plasma cholesterol from 416 to 250 mg. per cent were accompanied by no parallel variations in edema. A cholesterol of 285 mg. per cent in Case 4 is accompanied by no edema, though marked edema is associated with a cholesterol of 172 mg. per cent in Case 1 and 238 in Case 9.

Table 2 shows 3 cases of chronic Bright's disease dying of intercurrent infection—2 of pneumonia and 1 of erysipelas. At the time of death the plasma cholesterol was over 325 mg. per cent in each case. This is in distinct contrast with the low value for cholesterol observed in 9 cases dying in uremia. Thus, while a high plasma cholesterol enables us to reassure the patient that uremia is not imminent, it does not preclude the possibility of death from causes other than uremia.

As in Table 1, so in this group, no constant relation is observed between the height of the plasma cholesterol and the degree of edema. Case 11 had a plasma cholesterol of 326 mg. per cent and practically no edema; the cholesterol of Case 10 was not significantly higher (385 mg. per cent) but the patient was markedly edematous.

TABLE 1.—SIMULTANEOUS DETERMINATIONS OF BLOOD UREA NITROGEN AND PLASMA CHOLESTEROL IN 9 PATIENTS DYING IN UREMIC COMA FOLLOWING RENAL INSUFFICIENCY OF PRIMARY OR SECONDARY CONTRACTED KIDNEY.

TABLE 1.—SIMULTANEOUS DETERMINATIONS OF BLOOD UREA NITROGEN AND PLASMA CHOLESTEROL IN 9 PATIENTS DYING IN UREMIC COMA FOLLOWING RENAL INSUFFICIENCY OF PRIMARY OR SECONDARY CONTRACTED KIDNEY.

Case No.	Age and sex.	Date.	Whole blood urea N_2, mg. %.	Plasma cholesterol, mg. %.	Plasma carbon dioxid combining power, vol. %.	Blood pressure.	Albuminuria.	Edema.	Total serum proteins, gm. %.	Blood count.		Remarks.
										Hb., %.	R.B.C., millions.	
1	23, M	12/22/30	18	667	...	168/98	++++	++++				
		5/28/31	49	555	...	174/102	++++	...	4.2			
		4/18/32	84	477	...	...	++++	...	5.4			
		5/31/32	108	436	...	...	++++	...	...	66	3.79	
		6/14/32	93	360	...	...	++++	...	...	..	..	Patient discharged after recovering from uremic symptoms.
		9/ 8/32	111	239	...	...	++++	...	...	52	3.12	
		9/29/32	153	264	...	...	++++	...	5.5			
		9/30/32	164	200	...	...	++++	...				
		10/ 2/32	171	172	25.8	240/144	++	++++	5.6	..	..	Died in uremia, 10/3/32.
2	46, M	1/31/30	17	158	...	...	++	±	...	69	4.23	
		4/15/32	58	242	...	...	...	±	6.8			
		4/18/32	85	245	...	...	++	...	6.0	105	4.61	Transfusion.
		4/21/32	98	208	...	...	...	±	6.2			
		4/23/32	93	199	...	...	...	...	6.5			
		4/26/32	95	174	...	...	...	±	5.9			
		4/30/32	100	150	...	...	...	±	...	...	...	Died in uremia.
3	28, M	9/ 6/27	20	184	...	230/130	+	0				
		1/10/28	115	112	...	...	...	...	4.7	70	3.52	
		1/16/28	238	83	25.8	172/88	...	...	...	..	..	Note extremely low cholesterol; died in uremia.
4	39, F	12/14/31	86	250	...	230/140	++	±				
		12/15/31	135	285	...	...	...	...	...	40	2.06	
		12/28/31	87	151	41.9							
		1/ 7/32	106	133	47.5	...	++++					
		1/14/32	87	129	...	...	...	...	...	26	1.84	
		1/20/32	86	141	...	...	...	...	...	...	...	Died in uremia.
5	38, M	5/ 7/25	47	240	...	182/118	+	0	...	..	..	Transfusion.
		7/13/26	64	120								
		10/ 2/26	130	182								
		10/18/26	124	164								
		10/25/26	184	149	33.4	166/86	...	±	...	..	..	Died in uremia.
6	42, M	3/13/31	110	180	30.5	238/132	+	...	...	41	2.38	
		3/17/31	124	144	26.8	210/166	+					
		3/20/31	153	165	34.3	194/112	+	...	...	..	..	Died in uremia.
7	40, M	10/13/24	151	...	...	184/110	+++	++	6.5			
		10/15/24	345	140	39.0	178/110	+++	++	...	..	..	Died in uremia.
8	23, M	4/24/31	218	260	26.8	178/130	+++	±				
		4/25/31	242	203	...	...	+++					
		4/27/31	264	167	...	...	+++	...	...	45	2.32	
		4/28/31	268	217	...	...	+++					
		4/29/31	276	178	...	...	+++	±	...	..	..	Died in uremia.
9	36, M	3/28/31	36	238	...	140/92	++++	+++				
		4/16/31	28	416	...	...	++++	+++				
		4/28/31	39	309	...	...	++++	+++				
		7/ 1/31	117	250	8.0	...	++++	+++	7.1			
		7/ 3/31	119	...	7.0	...	++++	+++	...	..	..	Uremic acidosis; last cholesterol 2 days before death.

The terminal blood urea nitrogen is above 80 mg. per cent in every case. A fall of the plasma cholesterol below 180 mg. per cent is observed in every case, except 1, at the time of death.

TABLE 2.—SIMULTANEOUS DETERMINATIONS OF BLOOD UREA NITROGEN AND PLASMA CHOLESTEROL IN 3 PATIENTS WITH CHRONIC DIFFUSE GLOMERULAR NEPHRITIS WHO DIED OF CAUSES OTHER THAN UREMIA.

Case No.	Age and sex.	Date.	Whole blood urea N, mg. %.	Plasma cholesterol, mg. %.	Blood pressure.	Albuminuria.	Edema.	Total serum proteins, gm. %.	Blood count.		Remarks.
									Hb., %.	R.B.C., millions.	
10	32, F	2/5/29	18	469	148/96	++++	++++	..	61	3.50	
		6/19/29	28	667	...	++++	++++	..	52	2.80	
		9/19/29	23	588	...	++++	++++	..	..	..	Transfusion.
		9/27/29	72	554	...	++++	++++				
		10/ 3/29	140	460	...	++++	++++	..	70	3.74	
		10/ 9/29	52	370	...	++++	++++				
		10/22/29	69	459	...	++++	++++				
		11/ 2/29	52	385	...	++++	++++	..	..	..	Died of pneumonia.
11	30, M	1/ 3/27	41	279	172/108	++++	±	6.4	55	2.90	
		4/29/27	27	242	...	+++	±	..	48	2.70	
		8/ 5/27	35	326	240/142	...	±	..	45	3.01	Died of pneumonia.
12	21, M	11/27/24	41	173	140/100	++	++++	3.5	..	..	Hematuria.
		12/ 2/24	36	231	128/94	++	++++				
		12/29/24	22	294	132/90	++++	++++	3.0			
		1/21/25	32	200	138/92	++++	++++	3.6			
		3/16/25	20	320	...	++++	++++	..	42	2.40	Erysipelas of the lower extremities and back began 3/27/25.
		3/30/25	30	352	...	++++	++++	..	..	..	Died of erysipelas.

The plasma cholesterol is above 300 mg. per cent in every case at the time of death.

Table 3 details a series of observations on the simultaneous whole blood urea nitrogen and the plasma cholesterol in 12 patients with chronic Bright's disease. These individuals, despite marked, moderate or slight elevations of the urea nitrogen, are alive and feeling well and, in most instances, carrying on their usual business or professional activities. The plasma cholesterol is over 200 mg. per cent in 10 of the 12 patients. This is in distinct contrast to the cases in Table 1.

As has already been pointed out, in 3 instances among the cases in Table 3 the blood urea nitrogen was actually as high or higher than that of some of the fatal cases. Nevertheless, these patients recovered from their pre-uremic symptoms and were able to return to work; the cholesterol at the time they manifested a high blood urea nitrogen, headache, vomiting, etc., was over 200 mg. per cent. (Of the 12 cases listed in Table 3, all but 1, Case 13, are alive today. Case 13, male, aged 19 years, lived 4 months after the last recorded date; he died elsewhere and we are unable to furnish the terminal data.)

It is significant that the patients who are doing well have a high plasma cholesterol although there is little edema. This is a group conspicuous for its elevated cholesterol, yet it is also characterized by little or no edema.

TABLE 3.—SIMULTANEOUS DETERMINATIONS OF BLOOD UREA NITROGEN AND PLASMA CHOLESTEROL IN 12 PATIENTS WITH CHRONIC DIFFUSE GLOMERULAR NEPHRITIS ALIVE AND DOING WELL.

TABLE 3.—SIMULTANEOUS DETERMINATIONS OF BLOOD UREA NITROGEN AND PLASMA CHOLESTEROL IN 12 PATIENTS WITH CHRONIC DIFFUSE GLOMERULAR NEPHRITIS ALIVE AND DOING WELL.

Case No.	Age and sex.	Date.	Whole blood urea N_2, mg. %.	Plasma cholesterol, mg. %.	Plasma carbon dioxid combining power, vol. %.	Blood pressure.	Albuminuria.	Edema.	Total serum proteins, gm. %.	Blood count.		Remarks.
										Hb., %.	R.B.C., millions.	
13	19, M	12/31/31	56	234	...	158/110	+++	±	...	59	3.90	Transfusion.
		6/10/32	113	212	...	...	+++	±	6.4	72	4.20	Discharged feeling fairly well.
14	26, M	1/ 8/32	89	243	...	...	++	0				
		1/10/32	95	186	...	150/102	++	0				
		1/13/32	97	206	...	...	++	0	...	..	..	Discharged; headache and vomiting relieved; feeling better.
15	17, M	6/13/32	96	227	...	...	+++	++	6.4			
		6/28/32	87	280	...	...	+++	++				
		7/ 9/32	(N.P.N. 120)	335	...	...	+++	++	...	52	2.49	Discharged; feeling better.
16	30, F	3/10/32	63	403	27.1	212/114	+++	+	...	34	2.26	
		3/17/32	61	291	38.1	188/120	+++	+	...	40	2.09	Hematuria.
		3/25/32	63	248	...	170/100	+++	+	...	32	1.50	
		4/19/32	75	280	...	180/115	+++	+	...	..	..	Signed release; feeling fairly well.
17	19, M	4/ 1/32	47	320	...	210/140	++	±	4.6			
		5/ 2/32	59	337	...	...	++	±	...	..	..	Vomiting; headache.
		6/ 3/32	59	297	...	...	++	±				
		7/ 8/32	56	256	...	...	++	±	...	..	..	Feeling fairly well.
18	27, M	9/29/30	39	244	...	149/116	+++	±	...	76	4.00	
		2/12/31	35	483	...	154/102	+++	±	...	72	3.40	
		12/15/31	53	470	...	146/96	+++	±	...	60	3.27	
		1/22/32	51	350	...	146/96	+++	±	...	60	3.28	
		4/14/32	44	174	...	150/104	+++	0	...	56	3.10	Living and at work 6 months after this determination.
19	46, M	4/ 8/32	31	338	38.1	162/92	+++	+++	6.2	52	2.34	
		5/ 7/32	53	507	...	...	+++	+++				
		5/31/32	43	375	...	...	+++	+++				
		10/ 3/32	23	372	...	...	+++	+	...	..	..	Feeling well.
20	44, M	4/24/26	16	201	57.9	130/90	+++	++++	6.9	82	4.20	
		7/ 3/26	24	150	...	134/96	+++	++++	...	75	..	Note low cholesterol but no elevation of urea nitrogen.
		6/ 6/29	19	300	...	...	+++	±	...	87	5.04	Discharged; improved; working.
21	50, M	7/13/32	24	300	...	146/96	++	±	...	75	4.30	
		7/26/32	20	320	...	154/106	++	±	5.5			
		10/ 5/32	23	257	...	124/96	++	±	...	84	4.47	Feeling very well.
22	24, M	5/ 5/28	22	179	...	202/132	++++	+++				
		5/16/28	18	226	...	...	++++	+++				
		5/25/28	29	161	...	...	++++	+++	2.5	..	..	Feeling very badly.
		6/ 6/28	26	300	43.8	...	++++	±	...	42	2.36	Discharged; improved.
23	19, F	2/16/32	39	395	...	...	++	±				
		5/11/32	49	212	...	...	++	±	...	..	..	Sudden drop in cholesterol; feeling badly.
		5/17/32	49	221	...	178/120	++	±	...	..	..	Discharged; feeling better.
24	61, M	5/27/26	30	240	...	176/100	++	±				
		7/28/26	34	133	...	141/70	++	±				
		9/16/26	20	240	...	172/76	++	±				
		1/ 4/27	32	166	...	166/72	++	±	...	..	..	Doing well.

Irrespective of the height attained by the blood urea nitrogen (in some instances higher than that found in the fatal cases shown in Table 1) these patients did well and occasionally recovered from their uremic symptoms. The plasma cholesterol, with few exceptions, was 200 mg. per cent or above.

TABLE 4.—THE CHOLESTEROL CONTENT OF THE PLASMA IN CACHECTIC AND ANEMIC NON-NEPHRITIC PATIENTS (TUBERCULOSIS, AMYLOIDOSIS, CARCINOMA, APLASTIC ANEMIA AND SUBACUTE BACTERIAL ENDOCARDITIS).

Case No.	Age, yrs.	Diagnosis.	Whole blood N.P.N., mg. per 100 cc.	Plasma cholesterol, mg. per 100 cc.	Remarks.
1	33	Bilateral caseous pneumonic tuberculosis	27	134	Duration of 4 yrs.
2	20	Bilateral caseous pneumonic tuberculosis; amyloidosis	..	133	Duration of 1 yr.
3	31	Tuberculous peritonitis	..	113	Duration of 2 yrs.
4	37	Unilateral caseous pneumonic tuberculosis; empyema	31	132	Duration of 3 yrs.
5	28	Bilateral caseous pneumonic tuberculosis	..	*Trace*	Duration of ½ yr.
6	28	Unilateral caseous pneumonic tuberculosis; empyema.	27	127	Duration of 7 yrs.
7	32	Bilateral caseous pneumonic tuberculosis; amyloidosis	30	127	Duration of ½ yr.
8	49	Adenocarcinoma of esophagus; marked secondary anemia	30	113	Hb., 17%; eryth., 1,790,000; corp. vol., 14.5%.
9	55	Aplastic anemia (Roentgen ray)	29	109	Hb., 26%; eryth., 1,400,000; lcts., 1900.
10	27	Subacute bacterial endocarditis; right upper and middle lobe pneumonia; right empyema; fibrinopurulent pericarditis	49	136	Hb., 63%; eryth., 3,090,000.

The marked hypocholesterolemia observed in non-nephritic patients with cachexia and anemia is evident from the cases cited above. In 1 instance (Case 5) the plasma cholesterol was so low that accurate colorimetric estimation was not possible.

Cases 20, 22 and 24 illustrate a point which deserves emphasis. At times in the course of the disease a low plasma cholesterol was reached (150, 161 and 133 mg. per cent, respectively). Yet, since this occurred when there was practically no nitrogen retention, no uremic symptoms were observed. One patient (Case 22) felt poorly when the cholesterol fell from 226 to 161 mg. per cent within 9 days, although the blood urea nitrogen increased from 18 to 29 mg. per cent. It would thus appear that *a low plasma cholesterol is prognostic of death in uremia in a case of Bright's disease only at a time when the blood urea is elevated;* at other times the cholesterol may fall without the threat of a fatal outcome.

Discussion. The general facts that a low or subnormal plasma cholesterol is associated with impending death in uremia in patients with advanced Bright's disease, while a high plasma cholesterol indicates a favorable outcome so far as uremia is concerned, have been discussed in the analyses of the 3 tables presented. There remains the consideration of the possible cause for the decreased plasma cholesterol observed in cases with a poor outcome.

Three main approaches suggest themselves: I. The existence of an inverse relation between the plasma cholesterol and some other blood constituent: (*a*) urea, (*b*) plasma proteins. II. The effect of cachexia. III. The effect of anemia.

I. (*a*) Since a low plasma cholesterol is observed in uremic subjects with nitrogen retention, it may be inferred that as one constituent (urea) rises, the other falls. This view has been expressed by Chauffard, Laroche and Grigaut[1] and by Schmidt.[2] Considering the various types of Bright's disease in their broad aspects, it is true that in those forms in which the blood urea nitrogen is normal or but slightly elevated are those in which the plasma cholesterol is high, *e. g.*, chronic diffuse glomerular nephritis with a "nephrotic" component. The converse, a low plasma cholesterol and marked nitrogen retention, is not as clear as this. Throughout the tables presented, it will be observed that fluctuations in the urea nitrogen content of the blood are often accompanied by inverse changes in the plasma cholesterol; at other times, the tendency to such an adjustment is offset by various compensatory factors which render it difficult to note such a relation uniformly. Recent investigations carried out in this laboratory have shown that an increment in the blood urea following the ingestion of urea by human subjects is often accompanied by a striking diminution of the plasma cholesterol;[15] this reciprocal relation, however, is observed more frequently experimentally than clinically.

(*b*) We were unable to observe any constant relation between the plasma cholesterol and the total plasma proteins. Van Slyke and his associates[16] found that the plasma proteins tend to rise before death from renal insufficiency; in many of our fatal cases a terminal rise was observed. It might be assumed that the cholesterol falls as the proteins rise in order to maintain osmotic balance (Fishberg[17]). Yet, in Table 3 total plasma proteins of 6.2 gm. per cent and 6.9 gm. per cent are accompanied by a high cholesterol, while an extremely low plasma protein (2.5 gm. per cent in Case 22) is associated with a decreased cholesterol (161 mg. per cent). A subnormal plasma cholesterol (83 mg. per cent; 112 mg. per cent) in Case 3, Table 1, is not accompanied by a high plasma protein content (as might be expected if the osmotic pressure adjustment theory held true) but in fact by a low value (4.7 gm. per cent). Thus, the possibility is suggested that other compensatory factors tend to modify and, at times, even nullify this inverse relation between the cholesterol and protein content of the plasma, which theoretical and experimental considerations would lead us to believe probably exists.

II. The hypocholesterolemia observed in uremia may represent the usual finding in cachexia.[18]

III. The low plasma cholesterol observed in patients with non-nephritic anemia (pernicious anemia, chlorosis, aplastic anemia, etc.) has been recorded by many observers. Muller[19] and Peters and Van Slyke[18] have recently reviewed the literature on this subject. Table 4 shows a representative group of 10 non-nephritic patients with marked cachexia and anemia. The extremely low

plasma cholesterol observed in such instances is evident from the protocol. It appears probable, therfore, that the diminished cholesterol content of the plasma observed in cases of Bright's disease dying of retention uremia may be due to such contributing factors as cachexia and anemia.

Conclusions. 1. In cases of chronic Bright's disease with marked nitrogen retention, a low plasma cholesterol foretells death in uremia. In most cases this low reading is observed at an appreciable interval before death; in rare cases such a level is found only about 24 to 48 hours before exitus.

2. An elevated plasma cholesterol indicates a good prognosis as to recovery from pre-uremic symptoms but does not preclude the possibility of death from causes other than uremia.

3. There appears to be no close relation between the height of the plasma cholesterol and the degree of edema in patients with chronic Bright's disease.

4. There is some clinical evidence of a reciprocal relation between the blood urea and the plasma cholesterol; at other times this relation is offset by other factors. A constant inverse relation between the plasma proteins and cholesterol was not observed.

5. The diminished cholesterol content of the plasma observed in cases of Bright's disease dying of retention uremia is probably due to such contributing factors as cachexia and anemia.

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ACCIDENTAL HYPODERMIC TRANSMISSION OF MALARIA IN DRUG ADDICTS.

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Two malarial patients, habitually taking heroin intravenously, entered Cook County Hospital in December, 1932. Neither patient had recently inhabited a recognized malarial district. Both denied previous attacks of chills and fever. One of the patients stated that many of his addict friends were similarly ill with chills and fever. However, they avoided hospital treatment for fear of reduction or withdrawal of their drugs. A laboratory technician, who had worked in this particular ward for 4 years, observed that he had never seen a malarial patient who was not a drug addict.

We suspected that the disease was accidentally transmitted when we learned of the non-sterile technique and the habit of group injection practised by the drug addicts. It is their custom to congregate in groups of 3 to 12 or more for administering the drugs. Heroin is most frequently used at present, due to the prohibitive cost of morphin. The drug is dissolved in tap water. The solution is drawn into a medicine dropper. Strips of paper are wrapped around the tip of the dropper so that the hypodermic needle can be attached. The first recipient inserts the needle into a vein, at which time blood flows back into the barrel of the dropper. Then, he injects his portion of the drug. The hypodermic outfit and remaining contents are then passed to others of the group, who repeat the process. The instruments are never sterilized.

Artificial transmission of malaria is common in the treatment of general paresis. Accidental transmission has occurred in blood transfusions as described by Korabelnikoff[1] and Decourt.[2] Wenyon[3] described the infection of 10 men with malignant tertian malaria by non-sterile administration of salvarsan. The apparatus consisted of a receptacle, rubber tube with glass tube window, and sterile needle. The needle was inserted, the receptacle lowered so that blood flowing back to the window indicated that the needle was in place. The needle, but not the tube, was changed for each injection. Netter[4] reported a similar case.

Knowing the above facts, we can assume that the methods in vogue among the addicts of Chicago would tend to the dissemina-

tion of malaria from those afflicted with the disease. We undertook this study, seeking evidence for the transmission of malaria among addicts by the hypodermic needle and the importance of this mode of spread.

Methods of Study. First, we attempted to examine as many addicts as possible for malaria. In spite of coöperation given us by 2 addict malarial patients whom we had treated, their friends refused to come for examination. Some feared legal retention and others withdrawal of heroin.

Second, thwarted in the first plan, we turned to the analysis of the case histories of all patients diagnosed as malarial in Cook County Hospital from January 1, 1925, to March 5, 1933.

We utilized the histories of 197 patients. Of these, the parasite was demonstrated in 163 instances. In the charts of the remaining 34 patients, none addicts, the typical history and course, the finding of a palpable spleen, and the immediate response to quinin therapy forbade their discard as non-malarial.

For purposes of study we found it convenient to divide the cases into the following three groups:

1. Those found to be addicts.
2. Those non-addicts who gave a history of recurrent attacks of malaria or primary infection most probably contracted in the South.
3. Those non-addicts who denied exposure outside of Chicago and its environs.

Analysis of Histories. In 170 histories a definite statement as to locality of possible contraction of malaria occurred. Of these, 112 patients, exclusive of addicts, undoubtedly contracted the disease in the Southern states. Thirty-eight patients, who were not found to be drug addicts, denied exposure outside of the Chicago area. Twenty were morphin or heroin addicts and only 1 of these could have contracted the disease in the South. Thus, we found, with one exception, that addicts with malaria did not give the usual history of onset or recent exposure in a recognized malarial district.

Figure 1 presents data as to the time of onset of malaria in the three groups comprising 170 patients. The onset in the addicts with malaria was quite evenly distributed throughout all months of the year. The onset in non-addicts, contracting the disease in Chicago, occurred only between July and October, inclusive. In those contracting the disease in the South or suffering recurrent attacks, the onset was most frequent in the summer and early fall months. Thus, we found the onset of malaria in drug addicts to show no seasonal increase, as in natural infection, but to occur as one would predict if the infection were accidental and artificial.

Figure 2 presents data as to the number of each group of malarial patients admitted to Cook County Hospital during each year studied. From 1925 to 1930, only the occasional malarial patient was found to be a drug addict. In 1931 and 1932, the number of

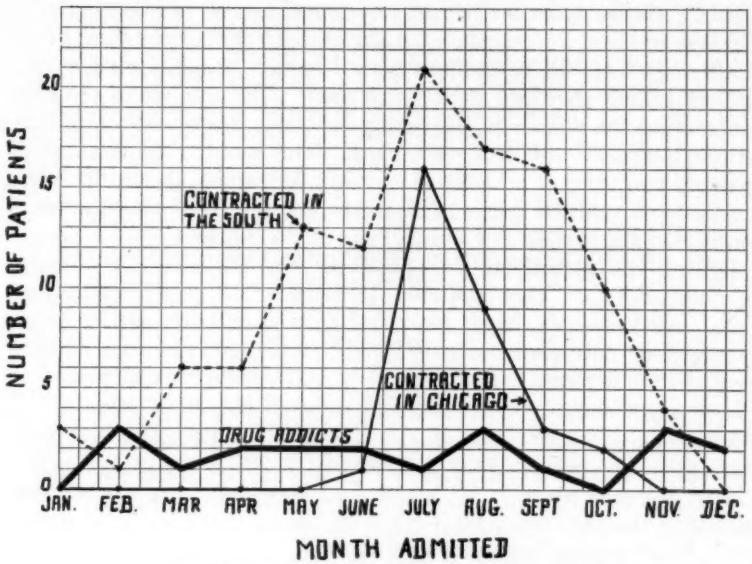

FIG. 1.—Month of onset of malaria in addicts and non-addicts.

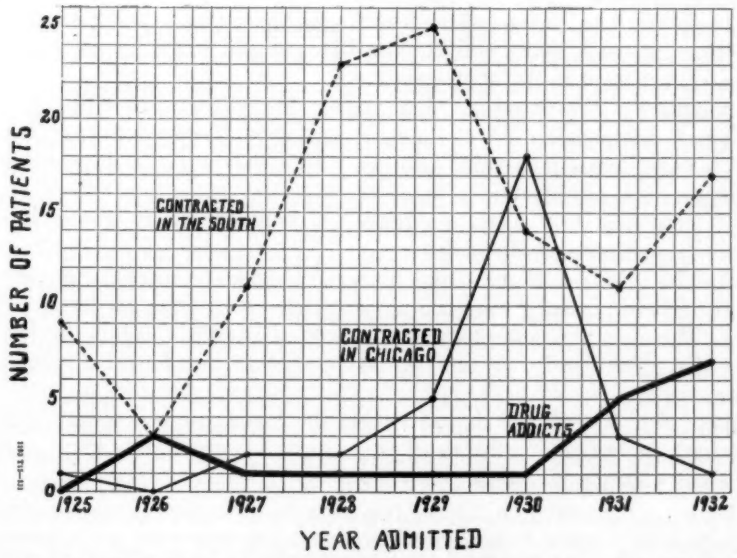

FIG. 2.—The total number of patients (nearest round numbers) admitted to Cook County Hospital during the years studied were as follows: 1925, 41,000; 1926, 41,000; 1927, 43,000; 1928, 48,000; 1929, 48,000; 1930, 50,000; 1931, 56,000; 1932, 63,000.

addict malarial patients definitely increased, out of proportion to the increase in total admissions. In the latter year 35 per cent of all adult male malarial patients admitted to this hospital were heroin addicts taking the drug hypodermically. The number of patients contracting the disease in the South definitely decreased after 1929, although total admissions increased. The number of non-addict patients contracting malaria in Chicago remained about the same except for a marked increase in 1930. In that year more patients contracted the disease in Chicago than in the South.

During the period studied, there were 20 histories of malaria in drug addicts. This included 17 patients, 3 being readmitted once. All habitually took morphin, heroin, or both, either intravenously or subcutaneously. The malarial parasite was demonstrated in every case. In 14 of the 17 patients it was identified as *Plasmodium vivax*. Seven patients suffered single infection and 7 others a double infection. In the charts of 3 patients, the specific identity of the parasite was not recorded. All patients were adult white males. Patient "A" knew 7 of the other 16 patients and admitted sharing injections with 4 of them. Patient "B" knew 5 and remembered injections with 2 of them.

In reviewing the literature, we found that Biggam,[5] in August, 1929, reported 10 cases of malignant tertian malaria in patients who habitually took heroin intravenously. All were inhabitants of Cairo, Egypt, where this type of malaria was "almost unknown" among non-addicts. Therefore, he concluded that the infection was conveyed by the use of unclean hypodermic outfits. Dr. Arafa,[6] writing in April, 1930, stated that Biggam and his colleagues had now observed over 100 such cases.

Summary. We present this paper to corroborate Biggam's original observation of the accidental hypodermic transmission of malaria among heroin addicts. The following observations support his conclusions:

1. The relatively high incidence of drug addiction among the malarial patients of our series.

2. The absence of the usual history of onset or recent exposure in the South given by malarial patients who were drug addicts.

3. The onset in addicts was distributed evenly throughout the months of the year, as one would predict of accidental artificial transmission.

We wish to call to the attention of American physicians this etiologic factor, which in recent years has become an important one at Cook County Hospital.

During the first 5 months of 1933, there have been 9 additional instances of malaria in the wards of Cook County Hospital. Of this number 1 was a woman and 8 were men. Six of these 9 cases were morphin or heroin addicts and only 1 of this group had been South. Of the 3 patients who were non-addicts 1 was a woman who apparently contracted malaria in Chicago and 2 were men who gave a definite history of the symptoms beginning in the South.

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THE CORRECTED SEDIMENTATION RATE (C.S.R.) IN SCARLET FEVER.

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Since 1918, when Fahraeus rediscovered the phenomenon of blood sedimentation, most of the vast literature concerning this subject has been devoted to its study in tuberculosis, rheumatic and gynecologic conditions. Relatively little has been published about the blood sedimentation test in acute infectious diseases, such as scarlet fever. The conflicting reports from Germany and the lack of a single American contribution to this subject prompted the author to investigate the blood sedimentation rate in scarlet fever.

Büchler,[1,2] in 1925, was the first to report on the blood sedimentation rate in this disease. In a series of 35 cases he found the fall of the sedimentation rate, repeated at regular intervals, so characteristic that he felt a differential diagnosis could be made by means of it. He called this typical curve the "Normal-Senkungs-Kurve" (N-S-K) and described it as gradually declining from an initially elevated level until it reached a normal figure on or about the 25th day of the disease. In cases which developed complications, there were aberrances from the typical curve and the return of the rate to normal would be delayed beyond the usual time. Unfortunately, nobody save Rohrböch,[3] with a series of only 8 cases, has been able to corroborate Büchler's results.

Rhodin's[4,5,6] findings in 70 cases differed greatly from those of Büchler. He felt that the curves all showed the following common characteristic: from a more or less elevated level, the curve suddenly descended to a considerably lower value, from which it ascended again to its previous position. This oscillation, called the "characteristic phase," recurred at intervals of 3 to 6 days, and through the presence of these phases the sedimentation curve ran in repeated and more or less regular waves. Rhodin further differentiated two types of curves: in the first, the rate gradually fell, reaching a normal level by the 4th to the 6th week or occasionally earlier;

in the second, the rate declined until about the 3d week and then showed a marked rise again. In both types of curves, however, the presence of the "characteristic phase" was manifest, and it was in this respect that the curve in scarlet fever differed from that found in other diseases.

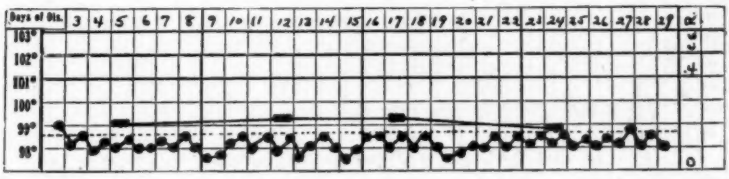
Other investigators have failed to corroborate either Rhodin or Büchler; Stoltenberg[7] could find no typical curve in 172 cases. Pulver[8] likewise failed to find a typical curve. He had cases in which there were no complications, where the rate was still elevated in the 6th week after the onset of illness. Wylie,[9] Rees Walton,[10] and Grenet, *et al.*,[11] make brief mention of the test in scarlet fever but present no cases in which the test was repeated at regular intervals.

Methods. In the present study, the technique of Rourke and Ernstene[12] was followed (rate of 0.35 mm. per minute as the normal limit). In a previous study,[13] the author raised this maximal normal value so as to include all readings up to 0.40 mm./min. Readings from 0.40 to 0.60 were termed moderately elevated; 0.60 to 0.90, elevated; and 0.90 and over, greatly elevated. The same standards are used in this study, save that readings 1 mm./min. and over are called greatly elevated.

Fifty-five cases of scarlet fever at the South Department of the Boston City Hospital were followed by means of the blood sedimentation rate, or more properly, the corrected sedimentation rate (C.S.R.). The patients ranged in age from 4 to 55 years. Each case had at least 1 weekly determination. The first few cases had 2 determinations during the first week of illness in an effort to see if there was any change in the C.S.R. with the disappearance of the rash. Inasmuch as no effect was noticed, this was not continued.

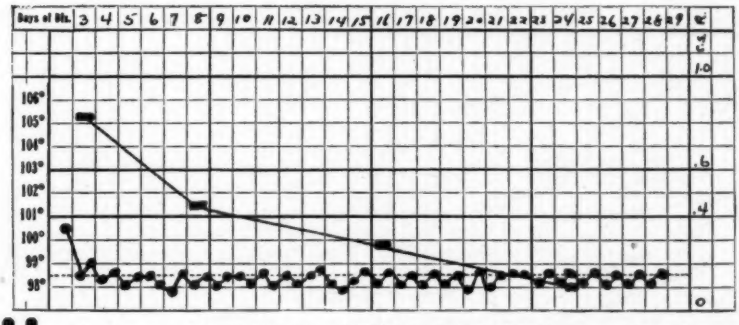
Results. Proper emphasis on the fact that the fall of the sedimentation rate depends a good deal on the severity of the case, does not seem to have been made by previous observers. Charts I to IV illustrate the typical course of the sedimentation rate in cases of scarlet fever ranging in severity from very mild to severe. In very mild cases, which show no fever or constitutional symptoms, there may be no elevation of the rate at any time. These cases are, however, uncommon. In ordinary mild cases, the curve shows the C.S.R. elevated at first, but falling fairly promptly and reaching a normal level during the second week of the disease. Save for the mild cases, the C.S.R. did not reach a normal level after the routine 4 weeks of hospital stay, even in uncomplicated cases. This agrees with Pulver's findings, where many cases showed elevated rates, even during the 5th and 6th week after onset. In only 12 of my 55 cases was the C.S.R. normal on discharge from the hospital. In Case 87919 (Chart III), a fairly typical moderate case of scarlet fever, the C.S.R. was somewhat lower on the 32d day than it was

on entry, but was still elevated. The rate in severe cases, as typified in Chart IV, remained at a greatly elevated level throughout the entire hospital stay. It may be seen, then, that there is no



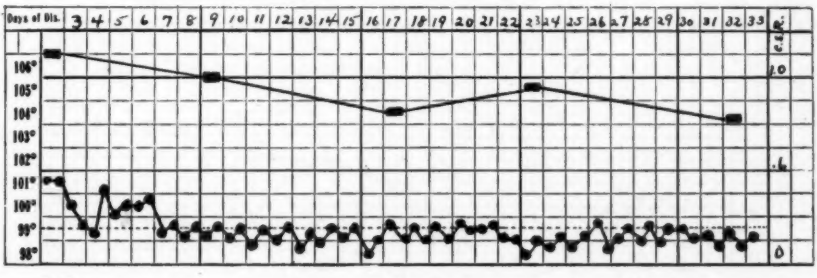
Temp. curve.
C.S.R.

CHART I.—Case 87965, M., age 10. Very mild, uncomplicated case of scarlet fever.



Temp. curve.
C.S.R.

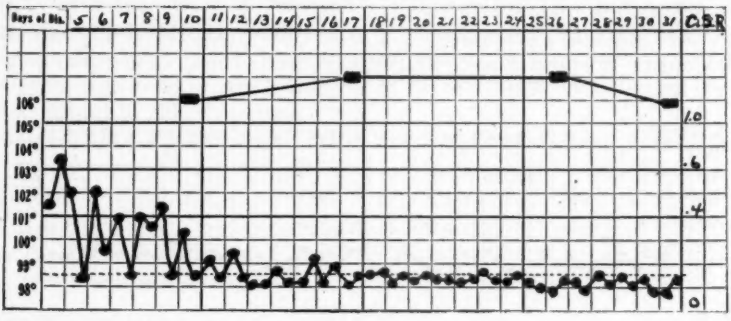
CHART II.—Case 87853, F., aged 8. Mild, uncomplicated case of scarlet fever.



Temp. curve.
C.S.R.

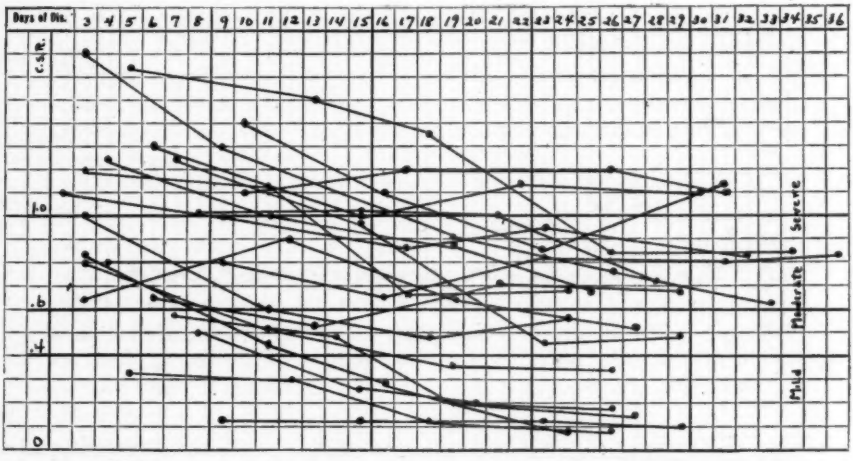
CHART III.—Case 87919, M., aged, 9. Moderate, uncomplicated case of scarlet fever.

typical curve for the decline of the sedimentation rate in scarlet fever, the curve depending greatly on the mildness or severity of the case. Chart V shows the variability of the curve in a series of uncomplicated cases ranging from very mild to severe. Obviously,



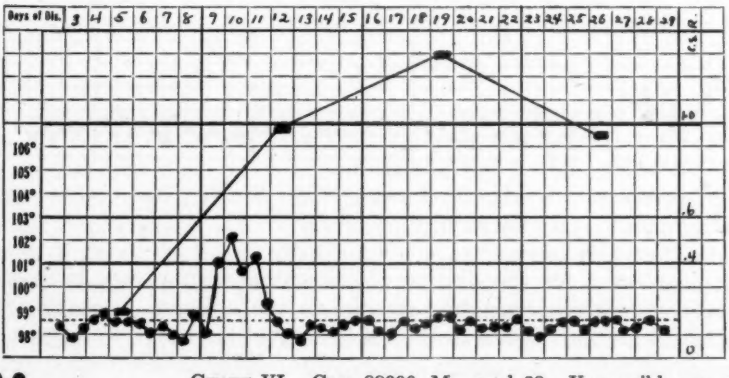
Temp. curve.
C.S.R.

CHART IV.—Case 88017, F., aged 26. Severe, uncomplicated case of scarlet fever.



C.S.R.

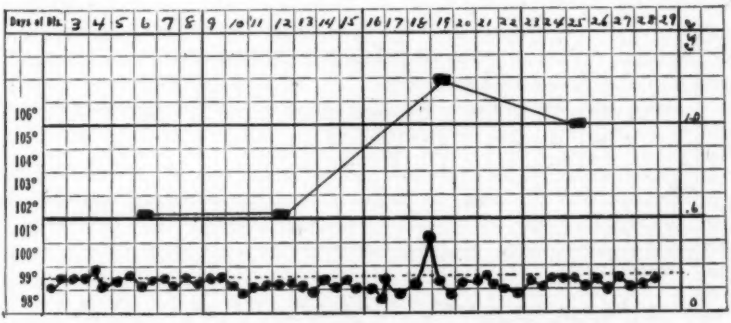
CHART V.—Uncomplicated cases of scarlet fever, showing variation in sedimentation curves.



Temp. curve.
C.S.R.

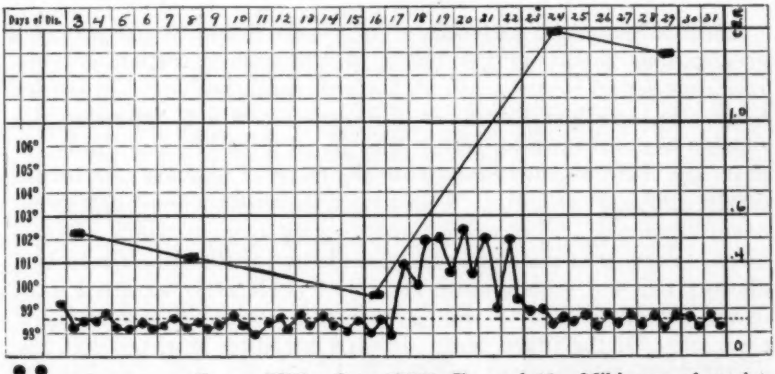
CHART VI.—Case 88006, M., aged 22. Very mild case of scarlet fever, complicated on the 9th day by a streptococcus sore throat.

then, as there is no typical curve, we cannot use it as a differential point. In fact, an ordinary streptococcus sore throat will give a sedimentation curve like that of a case of scarlet fever, as may be seen in Chart VI. At the onset of this very mild case, there was no fever and the C.S.R. was normal. The clinical course was complicated on the 9th day by a fairly severe streptococcus sore throat which produced a persistently elevated C.S.R., whose course certainly cannot be differentiated from the curve in a fairly severe case of scarlet fever.



Temp. curve.
C.S.R.

CHART VII.—Case 87995, F., aged 7. Mild case of scarlet fever, complicated on the 18th day by cervical adenitis.

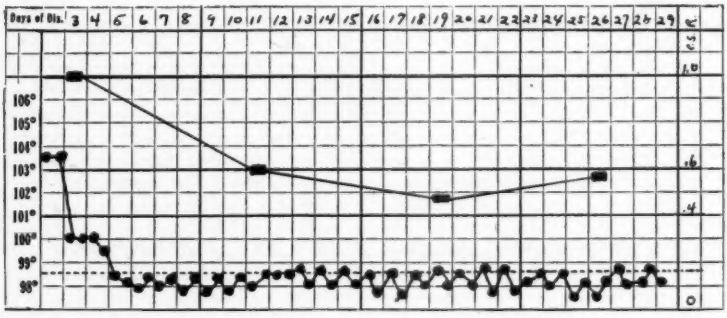


Temp. curve.
C.S.R.

CHART VIII.—Case 87860, F., aged 10. Mild case of scarlet fever complicated on the 17th day by a severe general arthritis.

Complications. The presence of a complication may be reflected in one of several ways in the sedimentation curve. If the C.S.R. is not too high or is falling, a complication, even though slight, will manifest itself by a distinct rise in the C.S.R., as may be seen in Chart VII. The onset of a cervical adenitis in the course of this mild case of scarlet fever caused a distinct rise in the C.S.R. If,

however, the rate is already high, the appearance of a complication may not produce any further change. Complications, of course, will keep the rate elevated much longer than it ordinarily would be. Büchler felt that the sedimentation rate began to rise several days before the onset of a complication and thus might serve as a warning signal. Stoltenberg could not confirm this. The author too, has not found that the sedimentation rate, as a rule, serves as a warning beacon before the complication actually sets in. As an example, in Case 87860 (Chart VIII) the C.S.R. was normal the day before the onset of a severe arthritis.



Temp. curve.
C.S.R.

CHART IX.—Case 87938, M., aged 23. Fairly severe case of scarlet fever treated with convalescent serum on 2d day of illness.

Effect of Serum and Antitoxin.—There have not been any previous observations made on the effect of the administration of convalescent serum or antitoxin on the sedimentation curve in scarlet fever. It is rather difficult in this series in which, following the regular hospital routine, serum was given to severe cases only, to draw any definite conclusions as to the effect of convalescent serum on the course of the C.S.R. Chart IX illustrates the most gratifying result obtained. This was a fairly severe case in which convalescent serum was given on the second day of illness. There is a distinct fall and maintenance at only a moderately elevated level in the C.S.R., which was not seen in any untreated case of equal severity. All the other serum treated patients, however, left the hospital with elevated or greatly elevated rates, and the course of the C.S.R. did not show any distinct fall. It was not possible to draw any conclusions at all as to the effect of antitoxin on the course of the C.S.R., as the few cases that received antitoxin all developed serum reactions which kept the rate elevated.

Comment. The most important practical question is naturally whether the determination of the sedimentation rate in scarlet fever is of any value to the clinician. I would say definitely that in comparison with chronic conditions such as tuberculosis or rheumatic fever where the sedimentation rate is highly important

as the best and frequently the only measure of activity, the determination of the rate in acute conditions, such as scarlet fever, is not of great importance or value. As a rule, the clinical picture in an acute illness, such as scarlet fever, is a sufficient guide. Possibly, in certain instances, for example, cases complicated by a general arthritis where the picture may greatly resemble rheumatic fever, regularly repeated determinations of the C.S.R. may be of value in evaluating the subsidence of activity. As for using the sedimentation curve as an aid in differential diagnosis, we have seen that the curve is far too variable to be of any assistance.

Summary. 1. Fifty-five cases of scarlet fever were followed by means of the corrected sedimentation rate (C.S.R.).

2. The curve of the sedimentation rate varied with the mildness or severity of the case. In the majority of cases, the C.S.R. had not returned to normal when the patients left the hospital.

3. Complications were manifested by a rise in the C.S.R. If the rate were already distinctly elevated, a complication might produce no further rise.

4. It was not possible to draw any definite conclusions as to the effect of the administration of convalescent serum or antitoxin on the sedimentation curve.

NOTE.—The author welcomes this opportunity to express his gratitude to Dr. Edwin H. Place, physician-in-chief, for permission to use the cases on his wards.

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THE INDUCTION OF EOSINOPHILIA IN NORMAL ANIMALS.

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MARKED eosinophilia has been observed as a symptom of many diseases, such as asthma, ankylostomiasis, filariasis, trichinosis and serum sickness. During the course of numerous acute infections,

the relative number of eosinophils fluctuates; the appearance of eosinophilia, according to Schilling,[1] indicates a favorable prognosis. The induction of eosinophilia in normal animals, therefore, may lead to an understanding of its relation to pathologic states.

Many workers have induced eosinophilia experimentally. The literature of the earlier attempts with worm extracts was ably reviewed by Wells[2] in 1920. In 1925, we reported[3] a high eosinophil count occurring in a rabbit in which the trachea was obstructed and attributed it to a disturbance in the acid-base equilibrium of the body fluids, a view that the recent literature would seem to support.

Pescatori,[4] who considered all types of eosinophilia to be characterized by asphyxia, induced the condition locally in the extremities by constriction; ½ hour after normal circulation was restored, he found an eosinophilia of from 4 to 9 per cent. When a general asphyxia was induced by injecting fluid into the trachea, the eosinophils rose from 12 to 30 per cent.

Vacca[5] fed copper sulphate to guinea pigs over considerable periods of time and found a marked increase in the eosinophils. He attributed this action to the copper ion, disregarding any possible effect which the acid radical might have had on the acid-base equilibrium.

Hajós, Németh, and Enyedy[6] increased the eosinophil count in 8 out of 10 rabbits by stimulation of the vagus nerve with Faradic current for from ½ to 8 hours. In their protocols, the authors record the fact that all of their animals were "very dyspneic" or "nearly dead" after 1 hour of stimulation. Aside from the authors' conclusions concerning this experiment, it is very evident from their data that profound changes must have occurred in the rate of elimination of carbon dioxid to produce dyspnea and death.

Numerous reports have appeared in recent years on the use of the barbituric-acid derivative called "nirvanal" in the treatment of chorea. Daily administration of this drug produces in man a syndrome called "nirvanal sickness," characterized by fever, an exanthematous rash, and a pronounced eosinophilia. De Rudder[7] has studied this peculiar condition and reports that the reaction of the urine is alkalin during the incubation period of the disease but becomes acid with the eruption of the rash, coincident with the appearance of a high degree of eosinophilia in the blood stream.

Among recent reports upon the experimental production of eosinophilia, there are 5 which have no particular bearing on the study that forms the subject of this paper, except for one common factor: each method has interfered with the elimination of carbon dioxid, or has altered the acid-base balance toward the acid side in some other manner.

It appears, then, that a disturbance in the acid-base equilibrium, either local or general, may produce a variety of changes in the blood and other organs. When an infection, toxin or drug, has an

opportunity to influence this system, it may upset the equilibrium. Deviations in the acid-base balance may be responsible for stimulation, growth, inhibition, or death of cells or cell groups.

Experimental Work. In this study of the effects of exposure to increased amounts of carbon dioxid, rabbits were used as experimental animals because of the facility with which they can be given intravenous solutions. It should be noted that the rabbit's polymorphonuclear leukocytes contain acidophilic granules and indeed some authors[8] refer to them as pseudo-eosinophils. All blood film preparations were allowed to dry in air, were then fixed and stained with Wright's stain, and were examined with an oil-immersion lens by artificial light.

The solution of carbon dioxid was prepared by bubbling the gas from a Kipp generator through 0.85 per cent sodium-chlorid solution, which was chilled by immersion in a pail of ice. The carbon-dioxid solution was kept in the refrigerator when not in use, and at other times on ice. It was standardized by titration with $\frac{N}{10}$ sodium hydroxid. After the syringes had been sterilized and chilled, the carbon-dioxid solution was drawn into them and they remained on ice until the injections were given.

In the second part of the work, the experimental animals were placed in a large museum jar, the wooden cover of which was held in place against a rubber gasket by a clamp. One ear of the rabbit was drawn through a hole in the cover in order that specimens of blood might be taken at frequent intervals. Moistened carbon dioxid was admitted through a second hole; through the third, there projected an outlet tube with a two-way stopcock which on one side communicated with the outside air and served to maintain atmospheric pressure in the jar and on the other was connected, by means of rubber tubing, with a gas burette. Samples of the air in the jar were withdrawn several times during each experiment and the percentage of carbon dioxid it contained was determined by absorption in normal sodium-hydroxid solution.

Results. The averages of the differential blood counts of 5 normal rabbits before the administration of carbon dioxid were as follows: 30.59 per cent polymorphonuclear leukocytes, 60.7 per cent lymphocytes, 3.3 per cent large mononuclears, 0.43 per cent eosinophils, 4.8 per cent basophils.

Table 1 gives the result of the first intravenous administration of carbon-dioxid solution. The eosinophil percentage increased from 0 to 2.5 in 30 minutes; 23 hours later, it was still high. Repetition of the experiment on the same animal on 2 successive days was without significant effect. In a fresh rabbit, the eosinophils were slightly increased after the administration of carbon-dioxid solution but they rapidly fell to normal (Table 2). Table 3 records a control experiment in which ice-cold salt solution containing no carbon dioxid was used.

In the second portion of the work, more encouraging results were obtained. In Table 4, figures for the first rabbit confined in the jar are given. No samples of air in the jar were collected during the first part of the experiment but the increase in the eosinophils was twenty-fold. The rabbit was removed from the jar when he lost consciousness and was replaced $1\frac{1}{2}$ hours later. Within 5 minutes, his eosinophil count rose to 8 per cent, 32 times what it had

been less than 2 hours before. The final concentration of carbon dioxid in the jar was 26.89 per cent. The relative number of eosinophils still remained high 24 hours later.

TABLE 1.—THE EFFECT UPON THE DIFFERENTIAL LEUKOCYTE COUNT OF THE INTRAVENOUS INJECTION OF 2 CC. OF PHYSIOLOGIC SALT SOLUTION CONTAINING 1060 MG. OF CO_2 PER LITER. (RABBIT NO. 3746.)

Time of cell count.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Large mononuclears, per cent.	Eosinophils, per cent.	Basophils, per cent.	No. of cells counted.
11.14 A.M.	33.0	57.0	3.00	0.00	7.0	436
During injection*	46.0	47.0	1.00	0.00	6.0	344
During injection*	56.0	51.0	1.00	1.00	1.0	267
11.29 A.M.	55.5	38.0	0.75	0.75	5.0	289
11.44 A.M.	49.0	43.0	0.50	2.50	5.0	451
10.00 A.M. (23 hours later)	43.0	49.0	5.00	0.90	2.1	328

* Two samples of blood were taken during the injection period, which required 1.5 minutes.

TABLE 2.—THE EFFECT UPON THE DIFFERENTIAL LEUKOCYTE COUNT OF THE INTRAVENOUS INJECTION OF 5 CC. OF PHYSIOLOGIC SALT SOLUTION CONTAINING 1000 MG. OF CO_2 PER LITER. (RABBIT NO. 3777.)

Time of cell count.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Large mononuclears, per cent.	Eosinophils, per cent.	Basophils, per cent.	No. of cells counted.
11.30 A.M.	33.0	56.0	4.5	0.6	5.9	318
During injection*	33.0	57.0	4.0	0.4	5.6	484
During injection*	38.0	52.0	4.2	1.0	4.8	282
During injection*	40.0	49.0	4.2	0.9	5.9	437
11.45 A.M.	50.0	36.0	4.6	0.4	9.0	433
12.00 NOON	43.0	47.0	3.2	0.3	6.5	217
1.20 P.M.	42.5	42.0	4.5	0.0	6.5	

* Three samples of blood were taken during the injection period, which required 1.5 minutes.

TABLE 3.—THE EFFECT UPON THE DIFFERENTIAL LEUKOCYTE COUNT OF THE INTRAVENOUS INJECTION OF 2 CC. OF PHYSIOLOGIC SALT SOLUTION CONTAINING NO CO_2.* (RABBIT NO. 3776.)

Time of cell count.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Large mononuclears, per cent.	Eosinophils, per cent.	Basophils, per cent.	No. of cells counted.
Control count	40.0	53.0	5.0	0.0	2.0	200
Injection begun	42.0	53.0	2.0	0.4	2.6	200
Injection finished	34.0	55.0	8.0	0.0	3.0	200
15 minutes later	40.0	52.0	6.0	0.0	2.0	200
30 minutes later	40.0	50.0	3.1	0.6	6.1	200

* 1.5 minutes were required for the injection.

TABLE 4.—THE EFFECT OF INCREASING THE CO_2 CONCENTRATION OF AIR UPON THE EOSINOPHIL COUNT. (RABBIT NO. 3778.)

Time of cell count.	CO_2* per cent.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Large mononuclears, per cent.	Eosinophils, per cent.	Basophils, per cent.	No. of cells counted.
Control count	....	27.0	65.75	4.5	0.25	2.5	341
2:02 P.M.	....	47.0	42.90	3.1	2.50	4.9	300
2:07 P.M.	....	51.0	33.20	3.8	5.10	6.9	250
		Intermission.†					
3:50 P.M.	11.68	41.0	49.00	3.0	3.00	4.0	235
3:55 P.M.	26.89	47.0	33.00	6.0	8.00	6.0	200
24 hours later	....	40.0	46.70	3.9	5.50	3.9	250

* Blanks indicate that the percentage of CO_2 was not determined.
† Rabbit lost consciousness and was removed from jar for 1.5 hours.

In a similar experiment with another rabbit, there was an initial rise in the eosinophils from 0.4 per cent to 1.7 per cent, followed by a drop to 1.4 per cent as soon as the animal was removed from the jar. There was a secondary rise to 3.4 per cent, which became apparent when a count was taken the next day.

Summary and Conclusions. 1. An elevation in the relative number of eosinophils was induced in rabbits subjected to increased carbon-dioxid tension in the blood, either by intravenous administration of carbon-dioxid solutions or by exposure of the animal to an atmosphere containing increasing amounts of this gas.

2. From this result, it is concluded that an alteration in the acid-base equilibrium of the body appears to incite an eosinophilia.

Further studies, it is hoped, will lead to a better understanding of the mechanism of this alteration.

I desire to express appreciation of the advice which I have received from Dr. C. C. Torrance throughout the work and in the presentation of the results.

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CHRONIC IDIOPATHIC HYPOCHROMIC ANEMIA.

ETIOLOGIC RELATIONSHIP OF ACHLORHYDRIA TO THE ANEMIA, WITH SPECIAL REFERENCE TO THE EFFECT OF LARGE DOSES OF IRON, ORGANIC (DIETARY) IRON AND OF PREDIGESTED FOOD UPON FORMATION OF ERYTHROCYTES.*

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DURING recent years the relationship between certain dietary factors and formation of erythrocytes has been demonstrated by Whipple[1] in the experimental anemia of dogs; and that of liver to pernicious anemia by Minot and his associates.[2] In addition, it has been clearly shown by Castle,[3] in his studies on the relationship of achylia gastrica to pernicious anemia, that it is necessary not only to ingest adequate amounts of food to insure proper nutrition, but also that it is equally essential that proper digestion and absorption of nutritional elements take place to prevent the development of certain deficiency states. One of the conditions in which there is a failure of the marrow to produce normal erythrocytes, and in which defective diet and improper function of the gastro-intestinal tract may be implicated, is chronic idiopathic hypochromic anemia.

Among patients with chronic hypochromic anemia will be found a group consisting especially of middle-aged women who subsist on a diet low in iron-containing food, and in whom gastric achlorhydria or hypochlorhydria is a constant feature. This condition apparently constitutes a distinct clinical entity. During the past few years, increasing numbers of reports of this condition have appeared in the medical literature, and have been classified variously as chronic chlorosis,[4] microcytic anemia,[5] simple achlorhydric anemia,[6] idiopathic hypochromic anemia[7] and by other

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We are indebted to Mrs. Katherine Purviance for the technical assistance on the blood.

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terms.[8, 9, 10] Although the mechanism which produces anemia in these patients is unknown, it seems plausible that it may be primarily dependent upon an abnormality in the metabolism of iron. It appears in some cases that the symptoms are intensified by chronic loss of blood, pregnancy,[11] or some other factor,[15] or following partial extirpation of the stomach. Since defective diet and achlorhydria or hypochlorhydria are constantly present,[12, 13, 14, 15, 16, 17] the questions arising for solution are: (1) is the anemia due to an inadequate intake of iron-containing foods? or, (2) is an abnormality of gastric digestion responsible for the anemia? It is the purpose of this paper to report the results of some experiments made in an endeavor to evaluate these factors by controlled observations on a series of 10 cases.

Method of Study and Nature of Cases. A gastric analysis was performed on the 10 patients. The amount of free hydrochloric acid as well as the total acidity were determined. The presence or absence of pepsin in the gastric secretion was estimated by the egg-albumen digestion method. An attempt to stimulate gastric juice secretion, following the removal of specimens of fasting content, was done by the oral administration of 50 cc. of 7 per cent alcohol, and, again, after the subcutaneous injection of 0.25 mg. of histamin.

All of the 10 patients studied were females. They ranged in age from 23 to 46 years. Some of the women had been pregnant, and one (Patient 10), with chlorotic anemia of pregnancy,[12] was 4 months pregnant at the beginning of our studies on her. One (Patient 8*) developed a hypochromic anemia after a partial gastric resection. She had been operated upon in 1914 and a gastroenterostomy performed, with the hope of giving relief from symptoms of peptic ulcer. In 1928 another operation was performed because the gastroenterostomy failed to function properly and, after removal of approximately two-thirds of the stomach, the remaining cardiac portion was anastomosed with the jejunum, thus leaving a blind pouch of the duodenum. Since then, the patient had been free of symptoms of ulcer but had developed a progressive anemia. In none of the patients was there a history of chronic loss of blood or recent infection, and in none could a malignancy be demonstrated as responsible for the anemia.

The anemia of all was distinctly chronic and of the so-called hypochromic type with a color index of less than one. Some of the patients were known to have been anemic for years and had been given various therapeutic preparations by mouth and injections of iron at varying intervals since childhood.

A history of all of the patients' dietary habits was elicited in a painstaking manner. Careful questioning revealed that the diet of all of these women was deficient in the amount of meats, fruits

* We wish to thank Dr. J. Homer Woolsey for permission to study this case.

and green vegetables consumed. The total calories, composed mostly of carbohydrate foods, were apparently adequate, for, with the exception of 3 women who were undernourished, they were all of normal weight or were overweight. Most of the patients seldom ate meat or eggs; others partook of these products perhaps on an average of 3 times a week in small portions. In most instances the patients stated that their dietary habits had been irregular since childhood and that their appetites were usually appeased with starchy foods and small portions of fruits or vegetables. One of the outstanding characteristics of the diets was the lack of iron-containing foods.

Throughout certain phases of the observations, total red cell counts and hemoglobin determinations were made at weekly intervals, and, during other phases of the experiments, daily examination of the blood was done including reticulocyte counts. The hemoglobin concentration was determined with a Sahli hemometer, with tubes calibrated so that 100 per cent equalled 17 gm. of hemoglobin per 100 cc. of blood.

TABLE 1.—CLINICAL DATA.

Patient No.	Sex.	Age.	Nature of case.	Gastric secretion.
1 . . . (I. G.)	F	42	Defective diet for years; twice pregnant; overweight	No free HCl after histamin; peptic activity normal.
2 . . . (M. H.)	F	27	Defective diet; undernourished; recent pregnancy	No free HCl after histamin; peptic activity normal.
3 . . . (L.)	F	36	Defective diet; normal weight; twice pregnant	No free HCl after histamin; peptic activity normal.
4 . . . (D. C.)	F	36	Deficient diet; undernourished; "anemic" since childhood; three times pregnant	No free HCl; 15 cc. N/10 acid per 100 cc. gastric juice after histamin; peptic activity normal.
5 . . . (M. W.)	F	46	Defective diet; known to have been "anemic" 5 years; normal weight	No free HCl after histamin; peptic activity normal.
6 . . . (K. V.)	F	23	Defective diet; undernourished	No free HCl after histamin; peptic activity normal.
7 . . . (G. S.)	F	36	Defective diet; slightly overweight; "anemic" 4 years; twice pregnant	No free HCl after histamin; peptic activity normal.
8 . . . (A. H.)	F	46	Gastroenterostomy 1914 for peptic ulcer relief; gastric resection (two-thirds of stomach removed) and gastro-jejunostomy performed in 1928; since then has developed anemia; undernourished; once pregnant	No free HCl after histamin; peptic activity reduced.
9 . . . (V. McD.)	F	49	Defective diet; "anemic" for years; twice pregnant; overweight	Trace of free HCl after histamin; peptic activity normal.
10 . .	F	34	Dietary habits fair; four previous pregnancies; four months pregnant; known to have been "anemic" 9 years; underweight	No free HCl after histamin; peptic activity normal.

Observations. Data relative to the important clinical findings and the nature of each individual case are presented in Table 1. It is to be noted that the gastric analyses performed by the same technique on all of the 10 women revealed a complete absence of free hydrochloric acid in the specimens removed after the period of fast and after the alcohol administration. In one of the specimens removed from a patient following the subcutaneous administration of 0.25 mg. of histamin there was a faint trace of free hydrochloric acid, as shown by the slight color change of Töpfer's solution. One other patient showed a low concentration of free acid (15 cc. $\frac{N}{10}$ acid per 100 cc. of gastric juice) after the administration of histamin. Peptic activity of the patients' gastric juice was of high order in all cases. A piece of boiled egg albumen 5 mm. long and 4 mm. in diameter was completely digested in 24 hours. The characteristics, therefore, of the gastric juice in these patients are the absence or greatly diminished amounts of free hydrochloric acid and the presence of pepsin in normal amounts.

The Effect of Large Doses of Iron. Experience in the treatment of hypochromic anemia, as has been previously recorded by various authors,[4, 7, 14, 18] has shown that patients with this condition respond well to the oral administration of large amounts of various preparations of inorganic iron. The response of the bone-marrow is indicated by the appearance of reticulated (immature) erythrocytes in the circulating blood and by an increase in hemoglobin and number of erythrocytes.

In Table 2 are shown the responses of the hemoglobin and erythrocytes to 6 gm. of iron and ammonium citrate (U. S. P.) fed daily to 3 patients who were permitted to continue taking their regular diet. It is to be noted that the hemoglobin of these patients increased from an average low of 58 per cent to an average high of 88 per cent. It is to be emphasized that the improvement in the state of the blood occurred within a period of 30 days.

TABLE 2.—RESPONSE OF HEMOGLOBIN AND RED BLOOD CELLS TO 6 GM. OF IRON AND AMMONIUM CITRATE DAILY IN PATIENTS WITH DEFECTIVE DIET, GASTRIC ACHLORHYDRIA AND ANEMIA WHILE ON "REGULAR DIET."

Patient No.	Before treatment.*	At 30 days after iron therapy.*	One year after therapy.
1	3.9	4.47	5.18
	46	96	89
2	3.27	4.59	†4.07
	65	80	73
3	4.2	5.3	
	65	90	

* Red blood cell count (upper figure); hemoglobin, per cent (lower figure).
† Two years.

The exact duration of the beneficial effect derived from the above therapeutic procedure, once the medication is stopped, is not known.

A remission may be induced and may be expected to persist from a few months to a few years, depending upon the individual case. Relapse is prone to occur after therapy with iron is omitted. Patient 5 had a relapse 4 months after therapy was stopped, and Patient 2 in Table 1 had a similar experience 2 years after she had last received treatment for the anemia. This information concerning the tendency of the anemia to recur is of considerable importance, and would seem to support the idea that the condition may be due to deficient assimilation of iron.

The Ineffectiveness of a Diet Rich in Iron. Table 3 shows a series of determinations of erythrocytes and hemoglobin on a group of patients who were fed a diet rich in iron prior to the administration of large doses of iron. These patients were selected for this experiment because they were intelligent and highly coöperative. It is, of course, imperative in an experiment of this kind that food of the type and amount prescribed be ingested.

TABLE 3.—RESPONSES OF RED BLOOD CELLS AND HEMOGLOBIN TO DIET RICH IN IRON-CONTAINING FOOD, THEN TO 6 GM. OF IRON AND AMMONIUM CITRATE (U. S. P.) IN PATIENTS WITH GASTRIC ACHLORHYDRIA, DEFECTIVE DIET AND ANEMIA.

Patient No.	Before treatment.*	Days after feeding "iron-rich" diet.	Time indicated in previous column.*	At 30 days after iron therapy.*	One year after therapy.
4	4.0	60	3.79	3.89	4.81
	60		55	73	88
6	3.9	53	3.15	4.45	4.64
	55		60	92	92
7	3.5	60	3.5	4.84	4.94
	42		45	80	92

* Red blood cell count (upper figure); hemoglobin, per cent (lower figure).

The diet used in the experiment as an "iron-rich" diet was considered to be adequate in all dietary factors and to contain a large amount of organic iron. The breakfast consisted of 250 cc. of orange juice, 2 soft boiled eggs and 1 piece of toast with butter; the lunch and dinner were each comprised of a combined raw and cooked vegetable salad; 200 gm. of spinach; 200 gm. of beef protein, and, in addition, during at least 1 meal, a dish of apricots, potatoes, a French artichoke and a dish of carrots. This diet is calculated to yield between 16 and 20 mg. of iron daily. It is stated by Sherman[20] that a diet containing 10 to 12 mg. of iron daily is more than sufficient to meet the ordinary metabolic demands for iron. This diet, naturally, contains other metallic substances, among which may be mentioned copper and probably magnesium.

These 3 patients who partook of this diet rich in iron had hemoglobin estimations of 60, 55 and 42 per cent at the beginning of the observations and at the end of approximately 60 days the readings were 55, 60 and 45 per cent respectively. This, accordingly, represents no significant change. They apparently were unable to derive

from food the factor or factors essential to the production of hemoglobin.

The determinations of hemoglobin on the same 3 patients, followed throughout the second stage of the experiment, while they were given 6 gm. of iron and ammonium citrate (U. S. P.) daily, show an improvement similar to that induced in the first group of patients. The data presented in Table 3 show the determinations of hemoglobin made prior to therapy with iron, which were 55, 60 and 45 per cent, and again 30 days after treatment was started, wherein there was an increase to 73, 92 and 80 per cent respectively. It will also be noted that an increase in erythrocytes occurred.

It would appear to be shown by this experiment that a diet regarded as fully adequate in content of iron is not alone sufficient to restore the blood in these anemic patients. Only when large doses of iron were administered in addition to the "adequate" diet did they show satisfactory improvement in the blood.

The Rôle of Abnormal Gastric Function. The second important factor demanding investigation was the part played by the achlorhydria or hypochlorhydria in producing the anemia or in preventing its relief by adequate amounts of iron in the diet.

The probable rôle of gastric anacidity in the production of the anemia has been emphasized by various authors.[12, 13, 14, 15, 16, 17] Achlorhydria may favor the production of anemia, as has been previously suggested by Mettier and Minot.[14] The lack of hydrochloric acid or greatly decreased amounts of it in the stomach could lead to a relative increase of pH in the upper intestine, where iron is largely absorbed, and thus fail to render the contents suitable for assimilation of iron. It was shown in the experiments that iron is absorbed better from an acid than an alkalin or neutral buffered medium.

In the present experiments 4 patients were given a predigested meal over periods of 20 to 42 days. The patients in this group (Cases 5, 8, 9 and 10), all had an anemia of the hypochromic type. They showed on gastric analysis a lack of free hydrochloric acid but the presence of pepsin. Cases 9 and 5 corresponded in general to Faber's description of chronic chlorosis, and Case 8, being similar in type, occurred in a patient following partial gastrectomy, and in Case 10 there was chlorotic anemia of pregnancy.

The meal designated as the predigested meal consisted of 2 soft boiled eggs, 200 gm. of cooked spinach, and 300 gm. of lean beef-protein freed of fibrous tissue.* To this food were added 4 gm. of commercial pepsin and sufficient strong hydrochloric acid to adjust the H-ion concentration to pH3. The mixture was then allowed to digest in the incubator at 37° C. for approximately 6 hours. It was found necessary to adjust this material to pH5 before administra-

* This meal, when ashed and analyzed was found to contain 12.5 mg. of iron.

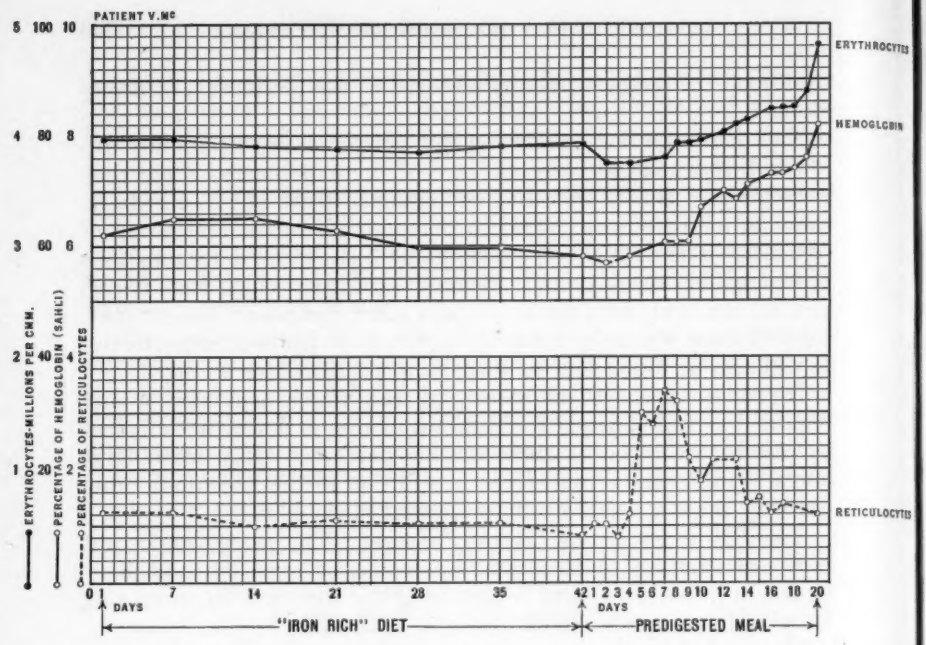

FIG. 1.—The ineffectiveness of an "iron-rich" diet on blood formation in Patient 9, but a satisfactory response to a "predigested" meal.

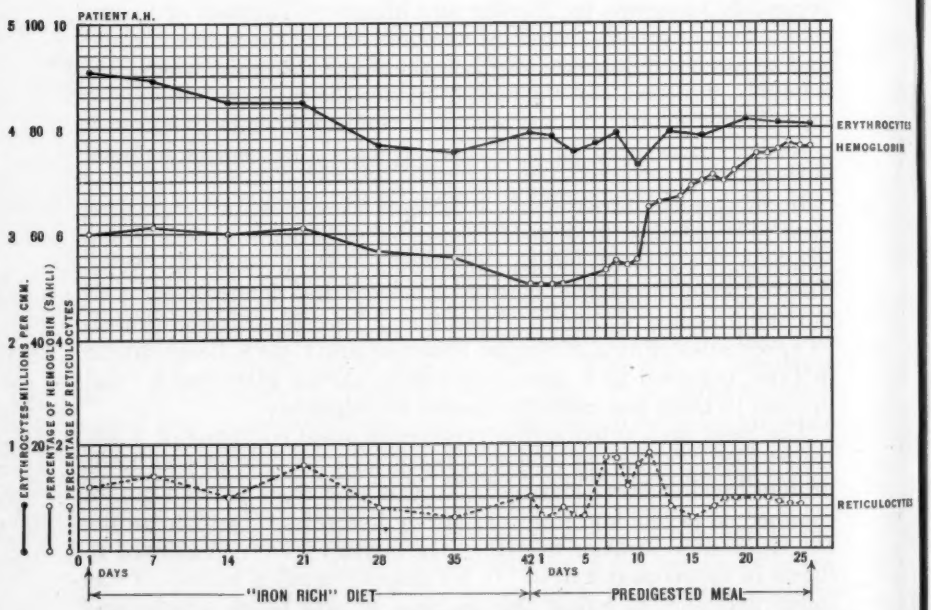

FIG. 2.—The ineffectiveness of an "iron-rich" diet on blood formation in Patient 8 with hypochromic anemia after partial gastrectomy, but a satisfactory response to predigested meals.

tion to the patient to prevent regurgitation. The meal was fed through a tube passed into the stomach. This replaced the evening meal.

As will be seen from an inspection of the data for these 4 patients shown in Figs. 1, 2, 3 and 4, there was a successful reaction to the "predigested meal" as indicated in the course taken by the hemoglobin and erythrocytes. This was in decided contrast to the failure of the blood to increase in numbers of erythrocytes or concentration of hemoglobin during the first period of observation in Patients 8 and 9 (Figs. 1 and 2), while on a diet rich in iron. In addition, it is to be noted that Patient 5 (Fig. 4), following a cessation of therapy with iron, had a relapse in her anemia in spite of the inges-

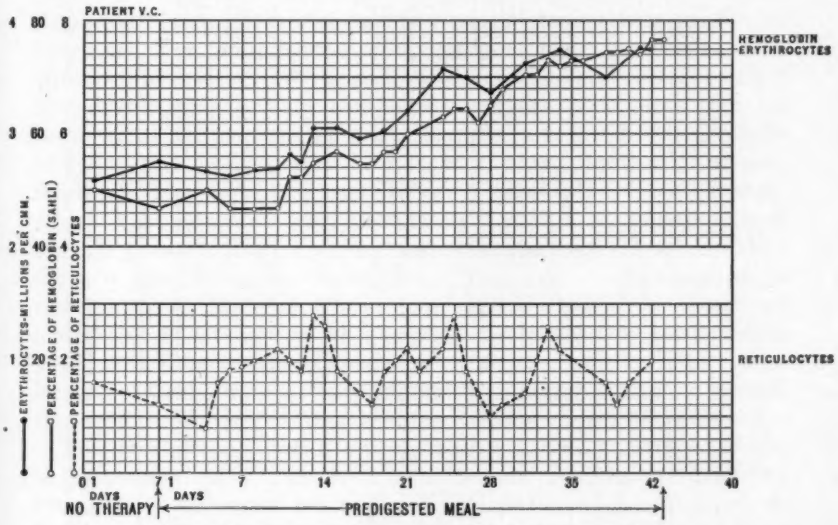

FIG. 3.—The effectiveness of predigested meals on blood formation in Patient 10 with hypochromic anemia of pregnancy.

tion of an iron-rich diet, but the observations made on this patient while being fed the "predigested meal" show a return of the blood toward normal.

It is interesting to note that the increased blood formation is not unlike that occurring in patients following adequate therapy with iron. Within 4 to 6 days after treatment was begun there was a response in the reticulocytes. This response in each case was one of slight degree, but it is to be emphasized that in each instance it was sustained 2 or more days, and was followed soon after by an increase in erythrocytes and hemoglobin. Obviously, one would expect that, since the hypochromic type of anemia is the one under discussion, the improvement in the blood would be chiefly a rise in hemoglobin rather than an increase in the number of cells.

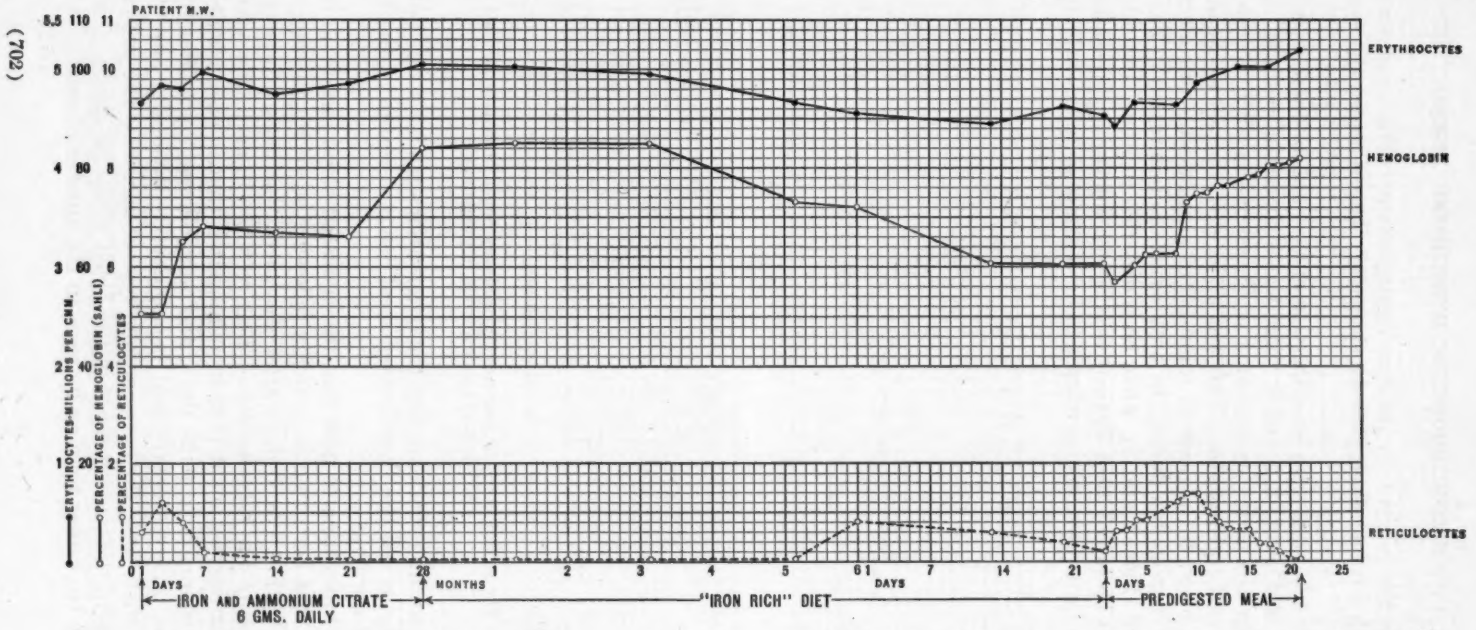

FIG. 4.—(1) A relapse of hypochromic anemia in Patient 5 after cessation of iron therapy; (2) failure of an "iron-rich" diet to maintain the blood in a normal condition; and (3) the restoration of the blood to normal following the ingestion of a predigested meal.

Discussion. The data obtained from the examination of the blood of 10 women with hypochromic anemia associated with gastric hypochlorhydria or achlorhydria serve to illustrate the changes which may take place in erythropoietic activity, depending upon therapy with inorganic iron; the administration of an iron-rich diet, and the feeding of a meal that had been digested *in vitro*. It was clearly demonstrated that patients with hypochromic anemia resspond well to suitable therapy with iron, and the results suggest that the defect in the red cells depends upon an abnormality in the metabolism of iron.

Since uncomplicated cases of hypochromic anemia will respond to large doses of iron, the question arises as to whether or not organic iron is as effective as inorganic iron. It has been repeatedly emphasized that large doses of iron are essential to insure a maximum response in the bone marrow, and that small doses have little or no effect unless injected into the subcutaneous or intramuscular tissues.[21] The administration of a comparable amount of organic iron (in terms of actual content of iron, from the point of view of intake in the diet) is not practical because of the large total mass of food required. However, if the daily requirement of iron is approximately 12 to 15 mg.,[20] then it may be assumed that if a similar amount of organic (dietary) iron, *i. e.*, 20 mg., were fed over a long period of time, it should replace the depleted body stores. If, under these circumstances, there is a failure to exhibit absorption of iron as expressed in production of increased percentage of hemoglobin, two possibilities arise to explain this defect: the first, that organic iron is not the factor necessary to hemoglobin production; the second, that iron is not derived from food due to some defect in digestion.

The data of the 3 patients presented in Table 2 and those of the patients recorded in Figs. 1, 2 and 4 indicate that organic (dietary) iron alone is either not available for assimilation or is not absorbed. On the one hand, it does not alleviate the anemia, and on the other, as shown in Fig. 4, it failed to maintain normal kinds and numbers of erythrocytes in the circulating blood. Of the 4 patients who were fed organic (dietary) iron previously acted upon by hydrochloric acid and commercial pepsin, the erythrocytes and hemoglobin returned to within normal limits. A somewhat similar observation has been recorded by Dameshek[22] who noted increased formation of red cells in a single case of hypochromic anemia after the administration of a meal digested with normal gastric juice. Assuming, then, that iron is one of the factors essential to erythrocytic production and especially to formation of hemoglobin, the experimental data presented here suggest that we are dealing with a type of deficiency disease wherein there is a failure to digest, assimilate and utilize iron in the food, and that the defective erythropoiesis is dependent upon abnormal digestive function. The altered formation of red cells would seem to be dependent upon the same mechan-

ism, so long as the presence of pepsin occurs in normal amounts, whether it be in patients with uncomplicated simple hypochromic anemia, hypochromic anemia of pregnancy, or in patients with partial gastrectomy.

Summary and Conclusions. Data are presented of studies made on the relationship of diet and nutrition to anemia in 10 cases of chronic idiopathic hypochromic anemia associated with hypochlorhydria or achlorhydria and defective diet.

The response of the bone-marrow, as determined by the hemoglobin and production of erythrocytes, to iron administered in large daily oral doses in the form of iron and ammonium citrate (U. S. P.) was compared to the response in patients on an "iron rich" diet. In addition, a comparison was made of the response of the bone marrow to a diet rich in iron and to a meal previously digested *in vitro* with hydrochloric acid and commercial pepsin.

The bone marrow responded rapidly and excellently to large doses of inorganic iron, but there was no evidence of increased hematopoiesis after the ingestion of an "iron-rich" diet for a long period of time. There was, however, a rapid and satisfactory increase in concentration of hemoglobin, production of red cells, and a slight reticulocyte response following the administration of predigested meals.

It is concluded, from these studies, that chronic idiopathic hypochromic anemia is one presumably due to a deficiency of iron wherein gastric dysfunction leads to failure in utilization of organic (dietary) iron.

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FETAL ENDOMYOCARDITIS: INTRAUTERINE INFECTION AS THE CAUSE OF CONGENITAL CARDIAC ANOMALIES.

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In the hearts of a number of infants who showed evidences of congenital heart disease at postmortem examination, we have found areas of fibrosis, cellular infiltration and calcium deposition. These changes, we believe, represent the end results of inflammatory processes which, in view of the age of the patients, must have occurred during intrauterine life. Such findings have led us to present the following series of cases with a general discussion of the subject.

Classifications of congenital heart disease usually list the various anomalies under two general headings: (1) those due to primary defective or arrested development, and (2) those due to infection transmitted to the fetus from the mother.

Several factors have been considered as possibilities in the first group. Certain instances are thought to be due to hereditary deficiencies in the germ cells whereby they are predestined to defective development.[1] Evidence for this may be suggested by associated congenital anomalies in other parts of the body. There are also included under this first heading those anomalies which are ascribed to the result of environmental factors which unfavorably influence the development of the growing organ. It has been suggested that chemical, physical or pathologic processes might interfere with the normal development of the heart during the early months when the septa are forming and the heart is assuming its final form. This would give rise to the gross departures from the normal mature form, such as the improper closure of one or more of the septa, anomalous origin of the great vessels, or perhaps one or more of the extreme types of maldevelopment, such as cor triloculare or cor biloculare.

The second group is made up of those instances in which the congenital anomaly is thought to be due to an infectious process involving the heart at some time after the third fetal month when the heart is believed to have assumed its adult form. In these cases the septa are free from defects, the essential relationships of the chambers

and great vessels are normal and the chief abnormalities consist of stenosis or atresia of the valves. It is this latter group of cases which is generally referred to under the heading of "Fetal Endocarditis." It is now generally accepted that myocardial changes are also of importance. This is emphasized by Abbott[2] who states that "careful investigation of the myocardium in most cases of atresia of the orifices, will reveal patchy yellowish-gray areas visible to the naked eye which microscopically show all stages of degeneration, vacuolation, fatty change and even, in a case under the writer's observation, calcification with cellular infiltration and a diffuse fibrosis which is often myxomatous in character."

Case Reports of Present Group. CASE 1.—C. W., white, male infant, age 36 hours. Cyanosis during last 12 hours. Fetal endomyocarditis; aortic atresia; hypoplasia of left auricle, ventricle, and ascending aorta; calcification of endocardium. Fibrosis of myocardium.

History. Patient was brought to the hospital on September 7, 1932, at the age of 24 hours, because of cyanosis noted for the preceding 7 hours. The mother and father, aged 24 and 27, respectively, were both in good health. Two siblings were in good health. There was no familial history of venereal disease. The essential features in the history are found in Table 2.

The laboratory test of significance here was a negative Wassermann reaction. Death occurred 5 hours after admission, and 36 hours after birth.

*Necropsy** (A-32-149). Performed 12 hours postmortem by Dr. Rew.

Heart. The heart weighed 25 gm. (normal for this age is 17 gm.). In the atrioventricular sulcus, and along the pulmonary artery and aorta were several small petechial hemorrhages beneath the epicardium. The right auricle was greatly distended. The pulmonary artery was much larger than normal. The aorta arose from a normal situation and gave off branches in the usual manner. However, the portion of it lying between the aortic orifice and the junction with the ductus arteriosus was small and cordlike with a marked decrease in its caliber. The ductus arteriosus was still patent, measuring about 6 mm. in length and about 6 mm. in diameter. The chambers of the right side showed nothing abnormal except dilatation and slight hypertrophy. The pulmonary valve measured 26 mm., and the tricuspid valve 48 mm. in circumference. The right ventricular wall measured 3 mm. in thickness. The left auricle was represented by a very small slitlike pocket measuring about 8 mm. in length. The mitral valve was stenosed and possessed thickened, partially fused cusps. It measured 12 mm. in circumference. The left ventricle was also a very small chamber measuring about 1.5 cm. in its longest axis, and 0.5 cm. in diameter. Its inner surface consisted of a thick, dirty white layer of endocardium about 2 mm. in thickness. The chordæ tendineæ were short and thick. The papillary muscles were indistinguishable. There was a complete atresia of the aortic orifice which was represented by a small pit where the aortic valve should be. The left ventricular myocardium which measured 6 mm. in thickness was of normal color, firm in consistency, and free from any evidence of scarring, inflammation or infarction. The right coronary artery appeared normal; the left was not located grossly. It was found only as serial sections were made through the point of atresia.

* In each case a complete necropsy was performed. Only the findings in the heart are described in detail. Other pathologic features are briefly summarized. No evidence of syphilis was found in the general viscera. Congenital malformations were limited to the heart.

Sections for microscopic study were taken from the wall of the right ventricle, including the tricuspid valve and a portion of the auricular wall; other sections were taken transversely across the left ventricle; serial sections were taken through the point of atresia of the aortic orifice. These were stained with hematoxylin and eosin, phosphotungstic acid with hematoxylin, aniline blue, and with Scharlach R for fat. The most outstanding feature of these sections was the enormous thickening and fibrosis of the endocardium of the left ventricle. Extending deep into the myocardium from the endocardium were bundles and tongues of connective tissue. The myocardium underlying this thickened endocardium showed degenerative changes in the muscle bundles, consisting of finely divided fat droplets dispersed throughout the muscle fibers. Nowhere was there cellular infiltration. Serial sections cut through the point of atresia showed small areas of calcification surrounded by cicatricial tissue. Von Kossa stains of these areas proved definitely the presence of calcium. The section from the right heart showed nothing unusual. *Further pathologic findings:* Terminal aspiration pneumonia; disseminated petechial hemorrhages; generalized vascular congestion.

CASE 2.—A. L., white male infant, aged 2½ months. Mother had "flu" during pregnancy. Cyanosis and convulsions since birth. Endocarditis (healed), cardiac hypertrophy.

History. The patient was brought to the hospital on October 9, 1932, because of "blueness," "failure to gain," and convulsive seizure since birth. (See Table 2.) Wassermann reaction was negative.

Necropsy (*A*-31–153) by Dr. Gross.

Mediastinum. Examination of the aortic arch showed an anomaly in that the right innominate and left common carotid artery arose together from the aortic arch.

Heart. The heart showed generalized hypertrophy. It weighed 70 gm. (normal weight for this age is 23 gm.). The hypertrophy was most marked in the chambers of the left side. The wall of the left ventricle measured 10 mm. in thickness; of the left auricle 3 mm. The aortic valve which measured 16 mm. in circumference, was stenosed, with thickened, partially fused cusps. Attached to the margins of the cusps were several small fibrous nodules. The mitral ring measured 32 mm. in circumference. Its valve leaflets showed no gross abnormalities. The endocardium covering the papillary muscles on the left was yellowish, thickened and sclerosed. The endocardium of the left auricle also showed a patchy distribution of yellowish thickening. The papillary musculature was scarred and suggested calcification. Elsewhere the myocardium showed no gross changes. The right side of the heart showed only a generalized hypertrophy. The right ventricular myocardium measured 6 to 7 mm. in thickness. The pulmonary and tricuspid valves appeared normal, measuring 24 mm. and 38 mm. respectively. The ductus arteriosus was patent, admitting a 2-mm. probe. The coronary arteries appeared normal.

Sections for microscopic study were taken from the wall of the left ventricle, the scarred papillary muscles, the mitral and aortic valves. These were stained with hematoxylin and eosin, phosphotungstic acid with hematoxylin, von Kossa's stain for calcium, and Scharlach R for fat. The myocardium of the papillary muscle and left ventricular wall showed the most interesting changes. There were many prominent scars consisting of dense connective tissue. There was a considerable amount of separation and hyalinization of the muscle fibrils with a slight, diffuse, cellular infiltration. The endocardium of the papillary muscle was thickened and fibrosed with a diffuse cellular infiltration. The underlying musculature was extensively scarred and showed small scattered areas of calcification. The sections of the aortic and mitral valves showed a generalized thickening, hyalinization and slight degree of cellular infiltration.

Further Pathologic Findings. Terminal bronchopneumonia, generalized passive congestion.

CASE 3.—L. C., male infant, aged 5 months, heart murmurs since birth, cyanosis, streptococcus hemolyticus septicemia. Pulmonary stenosis.

History. The patient was brought to this hospital for the first time on August 25, 1931, because of swelling of the right thigh and failure to move the right leg.

The mother of the patient had suffered since childhood from "heart trouble" which was presumably of a rheumatic type. She was very ill during this pregnancy with dyspnea, high blood pressure, nausea and vomiting. The first child was in good health; the second had anemia; the 3d pregnancy resulted in a miscarriage, the patient represented the 4th pregnancy. After the 3d pregnancy she was told she should not have any more children because of a "bad heart." The patient was born at full term by a normal easy delivery. The birth weight was 4 pounds 11 ounces. A diagnosis of congenital heart disease was made because of a loud blowing systolic murmur heard immediately after birth. Cyanosis was first noted at the age of 1 month. At this time the heart was slightly enlarged by teleoroentgenograms.

Death followed a streptococcus hemolyticus septicemia. The blood Wassermann reaction was negative. Teleoroentgenograms showed a normal heart shadow which was not enlarged for this age. The lung folds were clear.

Necropsy (A-31–132).

Heart. The heart weighed 30 gm. (normal weight for this age is 29 gm.). The left side of the heart showed no gross abnormalities. The mitral valve measured 34 mm. in circumference; the aortic 25 mm. The wall of the left ventricle was 8 mm. in thickness. The foramen ovale and ductus arteriosus were both closed. There were no septal defects. The aorta arose from a normal situation. The coronary arteries appeared normal. The branches of the aorta were anomalous in that the left common carotid and left subclavian both arose separately from the aortic arch.

The right auricle was slightly dilated, the right ventricle was dilated and hypertrophied. The right ventricular wall measured 7 mm. in thickness as contrasted with 2 to 3 mm. as the expected normal for this age. The tricuspid valve, which measured 32 mm. in circumference appeared entirely normal. The most important pathologic changes were found in the pulmonary valve which was stenosed, measuring 16 mm. in circumference. The cusps were thickened with opaque, yellowish, roughened surfaces. On the superior surface of the anterior leaflet was a fresh fibrinous vegetation, firmly attached to the valve surface measuring about 1.5 mm. in diameter. No further vegetations or thrombi were found elsewhere in the heart. The right ventricular wall was 7 mm. in thickness, as contrasted with 2 to 3 mm. as the expected normal for this age, and 8 mm. for the left ventricular wall. The myocardium was of a uniform reddish color with no gross evidence of fibrosis, degenerative or inflammatory changes.

Sections for microscopic study were taken from the left ventricular wall including the mitral valve, and from the right ventricular wall including the pulmonary valve with its vegetation. Diffusely scattered through the myocardium of both the right and left chambers were small, focal clusters of densely packed streptococci. No evidence of fibrosis was found in the myocardium. The pulmonary valve was thickened with a definite increase in the connective tissue elements. On its arterial surface was a small vegetation consisting of densely packed streptococci. The findings here represent old damage to the pulmonary valve with a superimposed fresh inflammatory process.

Further Pathologic Findings. Osteomyelitis of the right femur; bronchopneumonia; acute intracapillary glomerular nephritis.

CASE 4.—W. N., white male infant, aged 3 days, cyanosis and dyspnea since birth. Healed endocarditis with mitral and aortic stenosis.

History. The patient's birth was attended by the outpatient department of the Boston Lying-in Hospital. He was brought there January 22, 1931, on the 3d day of life because of cyanosis, dyspnea, and failure to nurse.

This was the 4th pregnancy of the mother, aged 32, who was in apparent good health at the time of delivery. Her family history and past history were entirely negative. Her first two children were normal and healthy. The 3d pregnancy was interrupted by a spontaneous miscarriage at the 5th month. During this pregnancy her course was normal except for a mild cold 2 weeks before term.

Death occurred several hours after entry.

Necropsy (A-32-94)*.

Heart. The heart weighed 28 gm. (normal for this age is 17 gm.). The right auricle and right ventricle were hypertrophied and moderately dilated, but otherwise not unusual. The right ventricular myocardium measured 4 to 5 mm. in thickness. The endocardium appeared normal. The pulmonary and tricuspid valves were also moderately dilated, measuring 2.7 cm. and 4 cm. in circumference. The chambers of the left side were much smaller than normal. The volume of the left ventricle was estimated at slightly less than 1 cc. Its myocardial wall measured 7 to 8 mm. in thickness and was somewhat less firm, but of the same color as the normal looking right ventricular myocardium. There were no areas of softening or fibrosis. Both aortic and mitral valves were markedly stenosed; neither admitted more than a 2-mm. probe. The cusps and leaflets of these valves were smooth, thickened, partially fused and free from vegetations. The entire endocardium of the left ventricle was yellowish in appearance and showed a diffuse and unusual degree of thickening. The chordæ tendineæ were involved in the same process, being thickened and shortened. The papillary muscles were indistinguishable as such, being obliterated by the cicatrization. The ductus arteriosus was markedly dilated, measuring 46 mm. in diameter. The foramen ovale appeared normal; it was patent with a valve covering $\frac{3}{4}$ of the opening, the latter being 2 to 3 mm. in diameter. The coronary arteries were normal.

Sections for microscopic study were taken from various portions of the walls of the four chambers, and from the mitral valve. These were stained with hematoxylin and eosin, eosin methylene blue, aniline blue, phosphotungstic acid with hematoxylin, and for fat with Scharlach R and hematoxylin. The most significant feature of these sections was the extreme thickness of the endocardium lining all surfaces of the left side of the heart. This was most evident in the endocardium of the left ventricle. Here the endocardial layer measured 1 mm. in thickness in contrast to the myocardium which averaged 3 mm. in thickness. The endocardium in these sections was even and regular, showing nothing abnormal except the generalized thickening. No irregular strands of connective tissue, cellular infiltration or increased vascularity were seen anywhere in the endocardium or myocardium. Sections of the mitral valve showed essentially the same features with a generalized thickening and hypertrophy of the connective tissue elements with no evidence of increased vascularity or cellular infiltration. The valvular endocardial surfaces were all smooth and regular, showing no evidence of either past or present vegetations.

Discussion. We have collected from the literature 10 cases to which we have added 4 of our own, making a total of 14, in all of which there is evidence indicating that the cardiac changes can best be explained on the basis of an infectious process originating

* Dr. A. T. Hertig kindly supplied the material for study in this case.

TABLE 1.—CASES OF FETAL ENDOMYOCARDITIS IN THE LITERATURE.

Serial No.	Source.	Age.	Mother's pregnancy.	Symptoms.	Valvular defect.	Associated pathologic changes (gross).	Histopathology.
1	Stiassny[3]	4 days	Not significant	Cyanosis—sudden death	Aortic stenosis	Endocardium of left ventricle thickened	Myocardial fibrosis and vacuolation.
2	Jacobsthal[4]	3 weeks	.....	.....	None	Calcification, right papillary muscle	Calcium deposition.
3	Ruge[5]	Premature	.....	.....	Aortic atresia	Hypoplasia of left vent. and aorta; endocardium of left vent. thickened	Myocardial fibrosis.
4	Mönkeberg[6]	4 days	Mother reported well	Cyanosis, dyspnea, sudden death	Aortic stenosis	Endocardium of left vent. thickened	Endocardial and myocardial fibrosis.
5	Kockel[7]	4 hours	Bronchitis 2 months before delivery	.....	Aortic stenosis; mitral stenosis	Endocardium of left vent. thickened	Endocardial fibrosis; myocardial degen. and calcif.
6	Ganeff[8]	1½ hours	Diarrhea in 8th mo.	No cyanosis	Mitral insufficiency	.....	"Verrucous endocarditis;" fibrous myocarditis.
7	Fischer[9]	5 weeks	"Influenza" 6 weeks before delivery	Cyanosis; edema of arms and legs	Aortic stenosis; mitral stenosis	Hypert. of both vent.; endocardium of left vent. thickened	Acute and chr. myocarditis with scarring and calcif.
8	Loeser[10]	40 hours	Mother reported well	Cyanosis; dyspnea	Aortic atresia	Hypert. of right vent.; hypoplasia of left vent. and aorta; endocardium of left vent. thickened	Endocardial thickening.
9	Von Zalka[11]	2 days	Not reported	.....	Pulmonary atresia; tricuspid stenosis	Hypert. of right vent.	Myocardial fibrosis.
10	Bellet and Gouley[12]	12 hours	.....	.....	Aortic atresia	Hypoplasia of left heart; myocardial scar	Myocardial scar.

TABLE 2.—AUTHORS' SERIES.

Age.	Mother's pregnancy.	Symptoms.	Heart signs.	Valvular defect.	Associated pathologic changes (gross).	Histopathology.
C. W. 5 mos.	Mother a cardiac patient	Terminal cough; edema and cyanosis	None	Aortic atresia	Hypoplasia of left auricle, vent. and aorta; endocardial thickening of left vent.	Endocardial fibrosis; myocardial fibrosis and calcif.
A. L. 2½ mos.	Mother confined to bed with the "flu" before term	Cyanosis; increasing convulsions	Heart enlarged; systolic and diastolic murmur heard best at base	Aortic stenosis	Endocardial thickening of left vent. and auricle	Cellular infilt., fibrosis and calcif. of myocardium.
L. C. 5 mos.	Mother a cardiac patient	Terminal cough; edema and cyanosis	Heart not enlarged; thrill and loud systolic apical murmur	Pulmonary stenosis	Secondary terminal acute streptococcus endocarditis	Old healed endocarditis and acute endocarditis and myocarditis.
W. N. 3 days	Two weeks before delivery confined to bed with a cold	Cyanosis; edema	None	Aortic stenosis; mitral stenosis	Hypoplasia and endocardial thickening of left auricle and vent.	Thickening of endocardium.

in intrauterine life. We have included in this series only those cases occurring in earliest infancy in which the gross pathologic findings have been supported by microscopic studies of sufficient adequacy to make them convincing. The cases selected from the literature are summarized in Table 1.

In the instances gathered from the literature, 8 died within the first 4 days of life. Of our own cases 2 died within the first 3 days, 1 lived 2½ months and the other 5 months. In the 2 latter cases there was clinical evidence of heart disease since birth. One had cyanosis since birth; congenital heart disease was recognized in the other because of a heart murmur heard since birth.

Knowledge concerning the health of the mother during pregnancy is inadequate. In 4 of the 10 cases from the literature, there is no information concerning the mother's health. In 2, the mother was reported well during pregnancy. One mother contracted bronchitis 2 months before delivery; another was sick with "influenza" 6 weeks before delivery.

In the present group one mother was entirely normal throughout the term of her pregnancy as far as we could learn. Another was a known cardiac patient but suffered no acute infection during her pregnancy. The mother of one contracted a mild upper respiratory infection of sufficient severity to confine her to bed 2 weeks before term. Another was ill with what was called "flu" 2 months before term. In only 2 of our group therefore was there any definite acute illness in the mother during pregnancy. These, together with 2 from the literature make a total of 4 in which there was a history of bronchitis, "influenza," or upper respiratory infection.

In regard to symptomatology, the most frequent finding throughout the series is cyanosis. Dyspnea and peripheral edema and other evidence of cardiac damage were found less frequently. Death often occurred unexpectedly.

Physical signs on examination of the heart which might indicate cardiac disease were not found in any of the instances in the literature. In our own group a murmur was heard in only 2 and only once was the heart enlarged to percussion. In the other 2 cases the hearts were clinically recorded as normal.

In regard to the pathologic features it is of importance here to emphasize only the findings indicating that in these cases the cardiac abnormalities represent the end results of old inflammatory processes. Of these findings, the most important are: (1) the gross distortion of the valves and the thickening of the endocardial surfaces, and (2) the microscopic evidence of previous infection, such as fibrosis and calcification.

Considering first the gross features, there was aortic stenosis in 7 of the total series. Five of these also showed changes in the mitral valve. One had pulmonary stenosis with a superimposed terminal acute bacterial endocarditis. In all the instances of steno-

sis, the appearance of the leaflets resembled the changes found in chronic valvular disease of later life. Aortic atresia occurred 4 times and pulmonary atresia once. In only 1 case were all the valves recorded as normal (Jacobsthal), but there was scarring and calcification of the myocardium. Associated with the primary valvular defects there may be secondary changes of varying degree. With aortic atresia, such changes are marked. The left ventricle serves merely as a functionless blind pocket communicating only with the left auricle. It is found to be small and hypoplastic. Similarly, the function of the aorta is only to carry blood to the coronaries by retrograde flow from the ductus arteriosus. Thus the aorta, too, is a hypoplastic structure. When the aortic orifice is narrowed rather than completely obliterated, the left ventricle is found larger than normal. In but 2 (1 of aortic atresia and 1 of aortic stenosis), although the endocardium was greatly thickened, the myocardium failed to show pathologic changes. In 4 cases calcium deposits were found in the myocardium. In 3, 2 from the literature and 1 of our own, the calcification was limited to papillary muscles of the left ventricle. In our case of aortic atresia the calcification was revealed only by making serial sections through the point of atresia.

In regard to calcification of the myocardium, there are 2 cases which deserve brief mention here. The first is a case recently reported by Diamond.[13] A mother who had been in good health was delivered during the 7th month of pregnancy of an infant, who died 30 minutes after birth. At necropsy extensive calcification was found in the right auricle and throughout the myocardium of both ventricles. The author ascribed this to the result of a "toxic necrosis of the myocardium" transmitted from the mother. We have observed an infant who was born normally of healthy parents, and who, on the 2d day, developed cyanosis and dyspnea. Death occurred on the 4th day. At necropsy a calcified mass was revealed, almost completely occluding the tricuspid orifice. Atheromatous changes were found in the coronary arteries. Such cases may properly belong in the category of fetal endomyocarditis. However, until more is known about the nature of these and similar cases, their pathogenesis must remain uncertain.

In considering the etiologic possibilities it is important to exclude congenital syphilis. In the cases from the literature,[4] syphilis has been definitely excluded in those reported by Mönkeberg, Loeser and Bellet and Gouley. In the remaining cases from the literature, exclusion must rest upon two factors: (1) the absence of other evidence of congenital syphilis in the body and (2) the nature of the cardiac lesion. Warthin[14] has shown that the prevailing lesion of congenital syphilis of the heart is a fibrous myocarditis harboring colonies of spirochetes. In the instances of congenital syphilis of the heart which we have encountered in the literature or in our

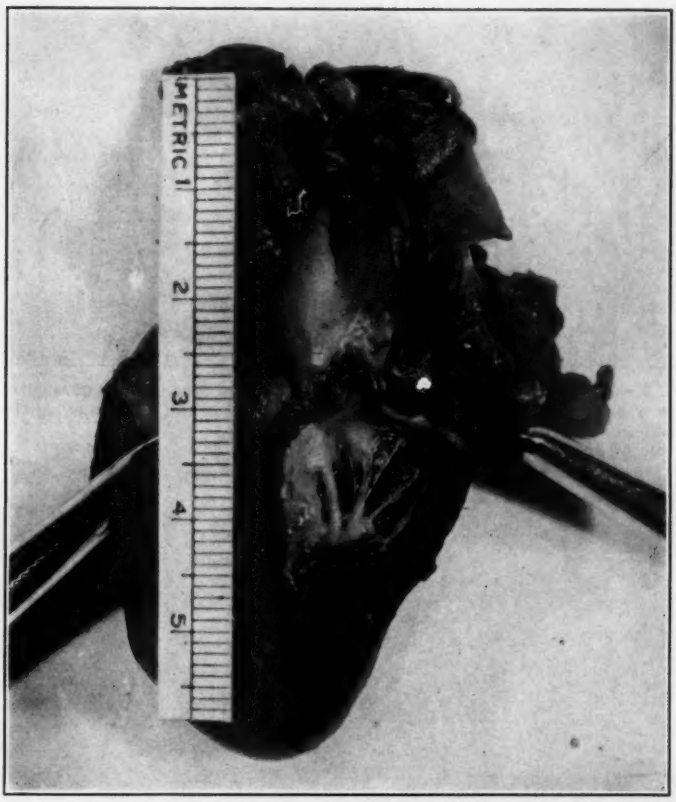

FIG. 1.—Photograph of heart in Case 4, showing left ventricle and aortic valve. Note greatly thickened endocardium and chordæ tendineæ.

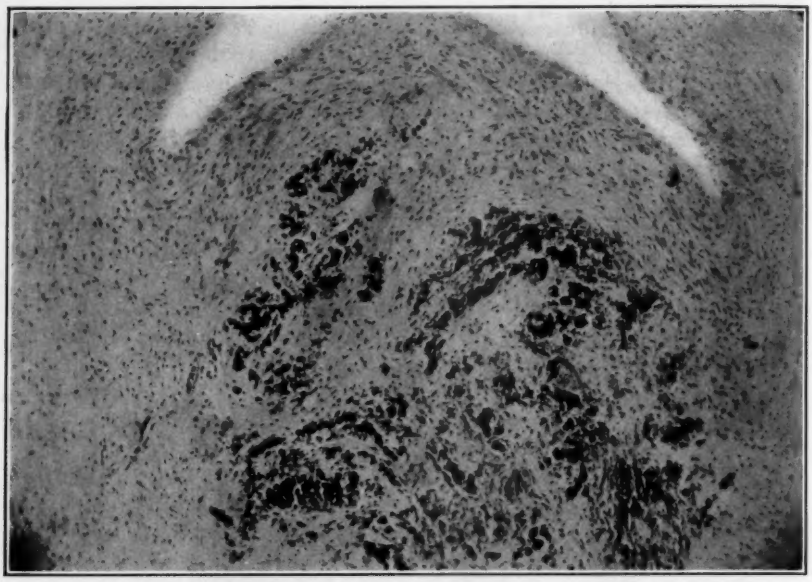

FIG. 2.—Photomicrograph of section through scarred area at base of aortic valve in Case 1, showing heavy deposits of calcium. Note lumen of aorta above. (Hematoxylin and eosin ×104.)

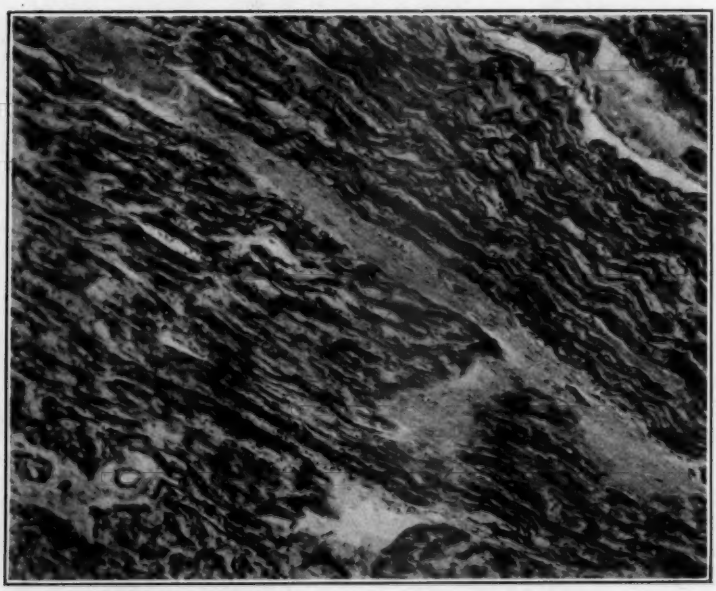

FIG. 3.—Photomicrograph of section through myocardium of left ventricle in Case 2. Note fibrosis in myocardium. (Hematoxylin and eosin ×118.)

laboratory, valvular lesions are conspicuously absent. In the series presented here, valvular stenosis and atresia are the prevailing lesions. Further negative evidence is furnished in our own group by the negative history of syphilis in the parents and negative Wassermann reactions obtained from the infant in each instance.

Of the nature of the infection in this series of patients or its mode of transmission we know little. In a few instances in this series, the mother contracted an "influenza" type of infection in the 7th or 8th month of pregnancy. It has been claimed that this was responsible for the cardiac changes in the infant. However, we know too little of the nature of such infections to be able to consider such a view as more than a stimulating suggestion.

It would appear profitable, as soon as a diagnosis of congenital heart disease is suspected, to make a careful review of the health of the mother during pregnancy, with particular emphasis on the nature, severity and time of occurrence of any acute infection. By this means information can be collected which may lead to an understanding of one of the causes of permanent and irreparable cardiac damage in the newborn.

Summary. 1. Fetal endomyocarditis as one of the causes of congenital heart disease is discussed.

2. A summary is given of 10 cases collected from the literature and 4 of our own, all free from evidences of congenital syphilis.

3. In each of the total series of 14 there is gross and microscopic evidence pointing to old infection. In view of the early death of each infant the infectious process must have occurred during intrauterine life. The nature of the infection is uncertain.

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RIGHT VENTRICULAR PREPONDERANCE (AXIS DEVIATION) OF THE HEART. THE SIGNIFICANCE OF VENTRICULAR PREPONDERANCE AND T-WAVE INVERSION IN THE HUMAN ELECTROCARDIOGRAM.

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At the New York Hospital and the Cornell Clinic the electrocardiograms of the last 4 years showing a right ventricular preponderance of the *Q-R-S* group were studied. This was done because it was thought that this type of electrical tracing would lead to observations on the right-sided enlargement of the heart. In 1929, attention[1] was directed to the electrocardiogram in arterial hypertension, a condition in which there is essentially left-sided enlargement. In summary, the record in arterial hypertension consisted of a left ventricular preponderance, or a left ventricular preponderance with T_1 inversion. It was concluded that these electrocardiograms were associated with an enlarged hypertrophied left ventricle and that the T_1 inversion was due to this anatomic change and not due to disease of the coronary arteries. It is thought that right ventricular preponderance alone, but more usually with T_3 or T_{2-3} inversion is a result of, or associated with, right-sided enlargement of the heart.*

The patients examined in this investigation had not received any digitalis at all or else the electrocardiograms were taken when digitalis had not been given for some time. Furthermore, the T-wave inversions were permanent abnormalities.

Among the 173 cases exhibiting right ventricular preponderance there were 99 (57 per cent) in which there was chronic rheumatic valvular disease (Table 1). In 7 of these 99 cases no specific valvular lesions were enumerated on the hospital charts, but in the remaining 92 cases mitral stenosis was present in each instance, either alone or associated with other lesions. In not a single case was aortic insufficiency the sole valvular lesion.

The degenerative type of heart disease composed the second largest group (Table 1). In this group there were 36 patients (21 per cent) who suffered from the following diseases: myocardial degeneration (11), arteriosclerosis (14), sclerosis or thrombosis of the coronary artery (7), hypertension (4).

* An interpretation of right ventricular preponderance was made when the main downward deflection in Lead I, that is to say, the S wave, was deeper than in either of the other two leads and the main upward deflection in Lead III (R wave) was taller than in either of the other two leads.

TABLE 1.—RIGHT VENTRICULAR PREPONDERANCE (173 CASES).

Diagnosis.	T-wave inversion.	No.	Per cent.	Sex.		Dead.	Roentgenogram.				Electrocardiogram.		
				M.	F.		Enlarged heart.	Left auricle and pulm. conus.	Lung markings and congestion.	X-ray missing.	Auricular fibrillation.	Changes P-waves.	Changes Q-R-S.
Chronic valvular disease	None	19	19	10	9	3 (16%)	8 (42%)	8 (42%)	7 (37 %)	2	2 (10½%)	6 (32%)	4 (21%)
	T_3	29	29	13	16	7 (24%)	14 (46%)	13 (45%)	13 (45 %)	6	6 (21 %)	9 (32%)	12 (41%)
	T_2 and T_3	48	48	20	28	18 (37%)	34 (71%)	27 (56%)	30 (62½%)	10	25 (52 %)	15 (31%)	21 (44%)
	Misc.	3	3	1	2	0	1	0	2	0	3	1	1
	Total	99	57	44	55	28 (28%)	57 (58%)	48 (48%)	52 (53 %)	18	36 (36 %)	31 (31%)	38 (38%)
Degenerative heart* disease	None	10	28	8	2	0	3	0	4	2	1	1	4
	T_3	6	17	5	1	0	0	0	2	3	0	1	4
	T_2 and T_3	18	50	11	7	7	9	1	11	7	6	1	10
	Misc.	2	6	2	0	0	0	0	0	2	0	0	1
	Total	36	21	26	10	7	12	1	17	14	7	3	19
Congenital	Total	3	2	2	1	0	1	0	0	0	1	1	1
Syphilis	Total	3	2	3	0	0	1	0	0	1	1	1	1
Non-cardiac†	None	12	38	11	1	0	0	0	1	2	0	2	1
	T_3	9	28	6	3	0	0	2	2	2	0	3	3
	T_2 and T_3	10	31	2	8	1	0	3	3	1	0	1	3
	Misc.	1	3	0	1	1	0	0	0	1	0	0	0
	Total	32	19	19	13	2	0	5	6	6	0	6	7
	Total	173											

* Myocardial degeneration (11), arteriosclerosis (14), coronary artery sclerosis or thrombosis (7), hypertension (4); singly in or combinations.

† Thyroid disease (7), emphysema, bronchial asthma or bronchitis (6), chronic tonsillitis (6), lobar pneumonia (2), tuberculosis of peritoneum (1), pleurisy (1), miscellaneous (9).

The 32 primarily non-cardiac cases consisted of 7 suffering from thyroid disease, 6 from emphysema, bronchial asthma, or bronchitis, 6 from chronic tonsillitis, 2 from lobar pneumonia, 1 from tuberculous peritonitis, 1 from pleurisy and finally 9 cases in which definite diagnoses were not made.

There were 3 cases of congenital heart disease and 3 cases of syphilis.

TABLE 2.—SUMMARY OF RIGHT VENTRICULAR PREPONDERANCE CASES.

T-wave inversions.	No.	Per cent.	Sex.		Dead.	Enlarged heart.	Left auricle, pulm. conus.	Increased vascular shadows.	X-ray missing.	Auricular fibrillation.	P-wave.	Q-R-S.
			M.	F.								
None .	41	24	29	12	3 (7%)	11 (27%)	8 (20%)	12 (29%)	6 (15%)	3 (7%)	9 (22%)	9 (22%)
T_3 only	47	27	27	20	7 (15%)	16 (34%)	15 (32%)	17 (36%)	11 (23%)	8 (17%)	13 (28%)	21 (45%)
T_2 and T_3 .	78	45	34	44	26 (33%)	43 (55%)	31 (40%)	44 (56%)	18 (23%)	31 (40%)	18 (23%)	34 (44%)
(Misc.)	7	4	4	3	1	1	0	2	4	3	2	2
Total .	173		94	79	37 (21%)	71 (41%)	54 (31%)	75 (43%)	39 (23%)	45 (26%)	42 (24%)	66 (38%)

A survey of the data obtained from the patients showing right ventricular preponderance (Table 1 and Figs. 1, 2, 3) yields information of clinical significance. Female subjects were more numerous in the group with chronic rheumatic valvular disease, but male individuals were in the majority in the cases with degenerative heart disease. All the cases have been subdivided into three divisions from an electrocardiographic point of view; those with no T-wave inversion, those with T-wave inversion in Lead III only, and finally, those with T-wave inversion in both Leads II and III. The summary will be analyzed in detail (Table 2). Of 41 patients with no inversion of the T-wave, only 7 per cent died, 27 per cent had enlarged hearts on the teleroentgenograms, 20 per cent showed a prominence in the region of the pulmonary conus and the left auricle, 29 per cent exhibited increased lung markings with suggestive vascular changes in the pulmonary vessels, 7 per cent exhibited auricular fibrillation, and 22 per cent showed *Q-R-S* abnormalities. In the next group with T_3 inversion alone, all the numbers became greater, that is to say, the mortality increased to 15 per cent, enlarged hearts to 34 per cent, bulge in the pulmonary conus region to 32 per cent, pulmonary vessel changes to 36 per cent, auricular fibrillation to 17 per cent, *Q-R-S* findings to 45 per cent. In the third subdivision (the cases with T_{2-3} inversions together) these numbers reach their maximum: Mortality 33 per cent, enlarged hearts 55 per cent, prominence of pulmonary conus 40 per cent, increased lung markings 56 per cent, auricular fibrillation 40 per cent, *Q-R-S* abnormalities 44 per cent. The conclusions to be drawn from these enumerations are these. Right ventricular preponderance with inversion of the T-waves in Leads II and III

is associated with the largest hearts, with the most frequent and most prominent bulge in the region of the left auricle and pulmonary conus, and with the greatest increase in tension in the pulmonary circuit. Clinically, it is the most serious lesion as shown by highest mortality rate and by high incidence of auricular fibrillation and *Q-R-S* changes. Next in severity is the right ventricular preponderance with only T_3 inversion and least in severity is the patient with right ventricular preponderance without any inversion of the T-wave.

An analysis of the findings in the patients who died reveals facts that are in harmony with the correlations previously made (Table 3). In the electrocardiograms of 37 patients who died the T-wave was inverted in Leads II and III in 32 cases, in Lead II alone 4 times only and the T-wave was upright in all leads only once. In other words, an overwhelming proportion of the patients who died exhibited inversion of T-waves in Leads II and III together. The Roentgen ray films emphasize the fact that these patients had enlarged hearts with prominence of the pulmonary conus.

TABLE 3.—FATAL CASES WITH RIGHT VENTRICULAR PREPONDERANCE.

	No.	Per cent.	Increased size heart.	Pulmonary conus.	Increased lung markings.	Mitral valve lesion.	Aortic valve lesion.	T-wave inversions.			Auricular fibrillation.	P-wave.	Changes Q-R-S.
								None.	T_3 only.	T_3 and T_2.			
No autopsy . .	24*	65	19	14	19	16	5	1	2	21	11	5	14
Autopsy . . .	13	35	12	10	12	11	6	0	2	11	3	3	5
Total . .	37		31	24	31	27	11	1	4	32	14	8	19

* No Roentgen ray picture in 5 patients.

The 45 patients suffering from auricular fibrillation showed many points of clinical importance. The mortality rate in this group was 33⅓ per cent, whereas the general mortality rate was 21 per cent. All the patients with auricular fibrillation under 50 years of age had a mitral stenosis. In short, a patient under 50 years of age showing a right ventricular preponderance and also auricular fibrillation, even though a diastolic murmur is not present, has in all likelihood mitral stenosis and the etiologic factor is probably rheumatic.

The frequency of abnormalities of the P-waves (31 per cent in the valvular disease cases) is to be attributed to the auricular hypertrophy, the result of mitral stenosis. The incidence of auricular hypertrophy may even be greater, since one-fourth of this group suffered from auricular fibrillation, a condition in which P-waves in the electrocardiogram disappear.

Discussion. In a survey of 235 normal adults (over 20 years of age) who were thoroughly examined at the Cornell University

Medical College during the last 5 years a right ventricular preponderance in the electrocardiogram was found only 3 times. This occurred in individuals with small or drop hearts. It is apparent that this electrocardiographic change should suggest that an abnormal or pathologic condition is present in the heart unless the heart in question is hypoplastic or pendulous.

It is clear that the electrocardiographic changes of right ventricular preponderance, right ventricular preponderance with T_3 inversion, or with T_{2-3} inversions, are closely related to the shape and size of the ventricles of the heart, particularly in reference to each other and with regard, of course, to the frontal plane of the body, the plane in which the electrocardiogram is led off. As the right ventricle enlarges, it makes up more and more of the anterior surface of the heart. Many factors come into play. Whether the conduction pathways in the right ventricle and pulmonary conus are lengthened and the muscle walls thickened, or their position changes, or the rate of passage of the excitation wave decreases, or the onset or the end of electrical excitation in the two ventricles is altered or whether a combination of any or all of these factors occurs, it appears that it is not primarily the anatomic condition of the heart muscle cell but rather the relation of the conduction pathways in the chambers which is important in the establishment of a right ventricular preponderance with T-wave inversion. Another bit of evidence to strengthen this view that the important factor is the position and shape of the heart chambers rather than the condition of the muscle fiber is the fact that of the 13 patients upon whom an autopsy was performed there were 3 in whom no evidence of myocardial damage was found on gross examination or microscopically and only 1 of the 13 had disease of the coronary vessels.

In the 13 postmortem examinations 12 very large hearts were found and in 10 cases the right ventricle was described as relatively more enlarged and hypertrophied than the left. This emphasis on right ventricular enlargement strengthens the belief that right ventricular preponderance with inversion of T_3 alone or both T_2 and T_3 is characteristic of right ventricular enlargement.

A great deal of clinical and experimental evidence has accumulated which substantiates the views which have just been expressed. Willius[2] found that preponderance of the left ventricle was often associated with negativity of the T-wave in Lead I or in Leads I and II, and right-sided preponderance with negativity of T_{2-3} and next with T_3. Barnes and Whitten[3] observed that in predominant left ventricular strain T_1 or T_{1-2} were inverted and in predominant right ventricular strain, T_{2-3}. From experiments also, similar facts are present. Using the heart-lung preparation Daly[4] found T_1 negative when excessive strain was placed on the left heart, that is to say, when the left ventricle performed work in excess (relative to the normal heart) of that of the right ventricle. In two experi-

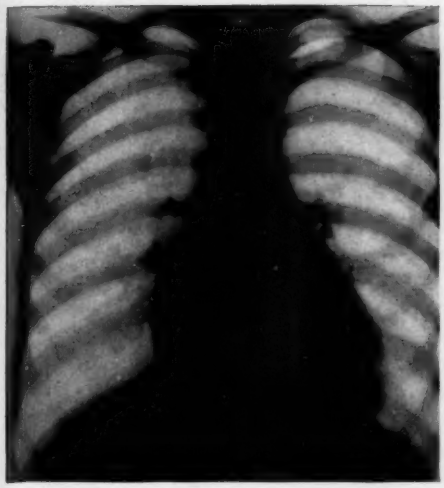

FIG. 1a

FIG. 1b

FIG. 1.—Case A. H. (584-297858), male, aged 16. Chronic rheumatic valvular disease, mitral stenosis and insufficiency: (*a*) roentgenogram March 10, 1931. Heart slightly increased to right and to left. Right auricular hypertrophy and enlargement of left ventricle. Prominence in region of left auricle and pulmonary conus. The lung markings are perhaps very slightly increased; (*b*) electrocardiogram March 11, 1931. Right ventricular preponderance; P waves large, indicating auricular enlargement; all T waves upright.

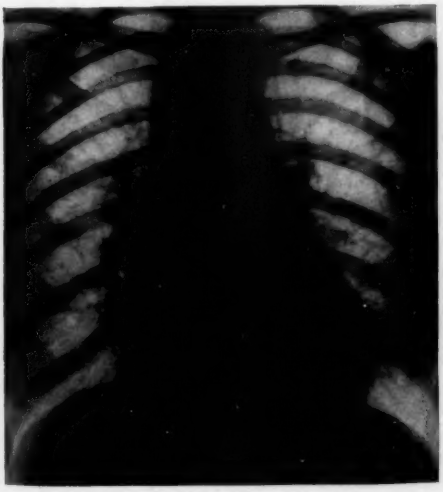

FIG. 2a

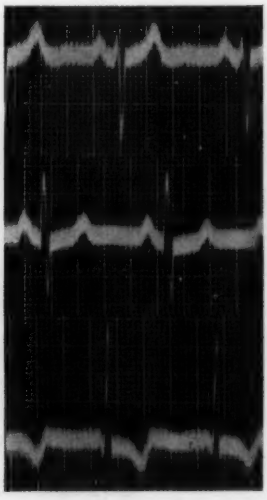

FIG. 2b

FIG. 2.—Case E. K. (71-286524), female, aged 24. Chronic rheumatic valvular disease, mitral stenosis: (*a*) roentgenogram May 24, 1929. Similar to Fig. 1 but more advanced. The heart is moderately enlarged, the right auricle is definitely hypertrophied, the bulge in the region of the pulmonary conus and left auricle more prominent. The lung markings are now moderately increased; (*b*) electrocardiogram May 25, 1929. Right ventricular preponderance, P waves large, inversion of T_3.

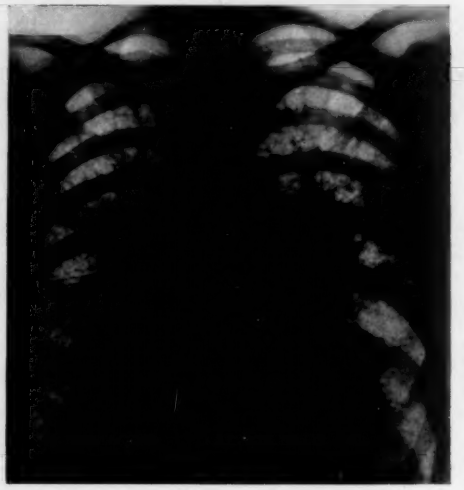

FIG. 3a

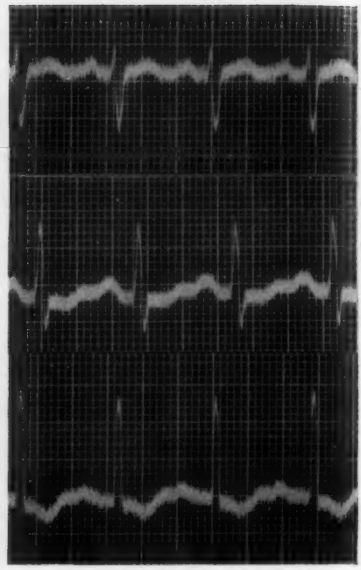

FIG. 3b

FIG. 3.—Case T. A. (9580-296363), male, aged 21. Chronic valvular disease, mitral stenosis and insufficiency, myocardial insufficiency, pulmonary infarct. Died January 1, 1931. (*a*) Roentgenogram December 4, 1930. Considerable enlargement of both ventricles, especially right. Huge bulge in region of pulmonary conus and marked accentuation of hilar and vascular shadows; (*b*) electrocardiogram December 4, 1930. Right ventricular preponderance; P waves large; semi-inversion of T_2 and inversion of T_3.

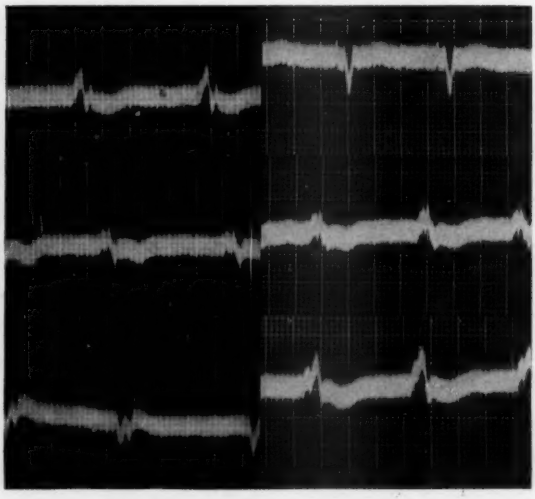

FIG. 4a FIG. 4b

FIG. 4.—Case S. L. (198-271006), male, aged 56. General arteriosclerosis, coronary artery disease, auricular fibrillation, myocardial failure. Died February 16, 1928. (*a*) Electrocardiogram February 21, 1927. Left ventricular preponderance, inversion of T_1 and T_2. (*b*) Electrocardiogram, same patient, February 2, 1928. Right ventricular preponderance, and now inversion of T_2 and T_3.

ments the pulmonary artery was partially occluded, and T_3 negativity was produced in 1 case and a diminution of T_3 positivity in the other. From an investigation of patients with myocardial insufficiency Winternitz[5] concluded that inversion of T_1 more than left ventricular preponderance was indicative of left ventricular hypertrophy and that T_3 inversion indicated right ventricular hypertrophy. He concluded that position and size of the heart chamber were the important agents in the production of inversion of the T-waves. He also cited the case of a man aged 59 suffering from myocardial degeneration and an enlarged heart who on maximal inspiration showed on the electrocardiogram right ventricular preponderance with T_{2-3} inversion, and on maximum expiration showed a left ventricular preponderance with a T_1 inversion. Since these electrocardiographic changes were not affected by vagal pressure or by the injection of atropin he concluded that change of position of the heart during respiration was the cause. He was of the opinion that a relation existed between left ventricular preponderance and T_1 inversion and right ventricular preponderance with T_3 or T_{2-3} inversions. Similarly, Pardee[6] found an inversion of T_{2-3} in 25 per cent of the records which exhibited right ventricular preponderance, and inversion of T_1 in about the same percentage of records showing a left ventricular preponderance.

If one ventricle becomes unusually enlarged or hypertrophied, absolutely or relatively to the other ventricle, the T-wave has a tendency to be directed oppositely to the main deflection.

Although the relative or absolute position, shape and size of the heart chambers may determine the ventricular preponderance and the T-wave inversion, functional or toxic effects which influence the conduction pathways on one side of the heart alone or relatively one more than the other, will undoubtedly also produce such changes. In the series of 173 cases there were 11 patients who at one time showed a right ventricular preponderance and at another a left ventricular preponderance. Although these changes were temporary, when a right ventricular preponderance was present T_3 or T_{2-3} were inverted and when the left ventricular preponderance was present T_1 was inverted (Fig. 4). This electrocardiogram was from a man aged 56, on whom a diagnosis of arteriosclerosis of the coronary arteries with myocardial degeneration and general arteriosclerosis had been made. The first electrocardiogram revealed a left ventricular preponderance and T_{1-2} inversions, and the second a right ventricular preponderance and T_{2-3} inversions. The patient was fully digitalized on both occasions.

The great number of abnormal P-waves in the records showing right ventricular preponderance is evidence of auricular hypertrophy, particularly of the left auricle, since the predominant valvular lesion in all these cases is mitral stenosis.

The presence of the degenerative heart conditions, such as disease

of the coronary artery, myocardial degeneration and hypertension, among those that produce right ventricular preponderance was unexpected. A left ventricular preponderance is usually found in these conditions. In occlusions of the coronary artery, however, the axis deviation often changes (Fig. 4). In conditions such as arterial hypertension in which the left side of the heart is primarily involved, after a long interval of time the right side finally shares the burden and the right ventricle then enlarges.

Summary. The position, size and shape of one ventricle with respect to the other can be correlated with deviation of the electrical axis (ventricular preponderance) and inversion of the T-wave. Right ventricular preponderance with inversion of T_3 alone, or of both T_{2-3}, is characteristic of right ventricular enlargement. Left ventricular preponderance with inversion of T_1 is characteristic of left ventricular enlargement.

The inversion of T_3 or both T_{2-3} is commonly associated with right ventricular preponderance. Inversion of T_1 is commonly associated with left ventricular preponderance.

A more or less permanent T-wave inversion is not necessarily indicative of a pathologic process in the heart muscle.

As one ventricle definitely hypertrophies and enlarges, the T-wave has a tendency to become directed oppositely to the main deflection.

The groups of diseases associated with right ventricular preponderance are, in the first place, chronic valvular disease (57 per cent), with mitral stenosis alone or associated with other valvular lesions; in the second place, degenerative heart disease (21 per cent); and in the third place, non-cardiac disease, such as thyroid disease, bronchial asthma and emphysema; and finally, congenital heart disease and syphilis. Female individuals predominated by number in the patients with chronic valvular disease, and male individuals were in the majority in the degenerative heart disease group.

Right ventricular preponderance with inversion of T_{2-3} is associated with the most marked right ventricular enlargement, with the largest hearts, with the most marked enlargement of the pulmonary conus and the left auricle, with markedly increased lung markings and congestion in the lungs and with the highest mortality (33 per cent). Right ventricular preponderance with inversion of T_3 alone is associated with a less marked degree of these anatomic changes and a mortality of 15 per cent, and finally in right ventricular preponderance without any inversion of the T-wave at all, the least changes occur and the mortality is only 7 per cent.

Auricular fibrillation was present in 40 per cent of the patients showing right ventricular preponderance with both T_{2-3} inverted; 17 per cent when T_3 alone was inverted; and only 7 per cent with no T-wave inversion. In a patient under 50 years of age exhibiting right ventricular preponderance and auricular fibrillation, chronic disease with mitral stenosis is probably present, whether or not a

diastolic or other murmur is heard, and the etiology is probably a rheumatic disease.

In chronic valvular disease right ventricular preponderance appears to indicate the presence of mitral stenosis. In a patient who has chronic valvular disease and right ventricular preponderance the diagnosis of aortic insufficiency as the only valve lesion is practically eliminated.

In electrocardiograms of patients suffering from chronic valvular disease which show right ventricular preponderance, abnormal P-waves are very frequent, due to the presence of auricular hypertrophy resulting from mitral stenosis.

In the same patient there may occur a change from a left ventricular preponderance with T_1 inversion to a right ventricular preponderance with T_3 or T_{2-3} inversion, or a change from right ventricular preponderance with T_{2-3} inversion to a left ventricular preponderance with T_1 inversion.

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THE EFFECT OF THE HEART'S POSITION ON THE ELECTROCARDIOGRAPHIC APPEARANCE OF BUNDLE-BRANCH BLOCK IN MAN.*

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(From the Heart Station of the Michael Reese Hospital.)

Katz and Ackerman[1] studied the effect on the electrocardiogram of changing the position of the heart in experimentally produced bundle-branch block. They found that a change in the heart's position caused a noticeable shift of the electrical axis. At times

* Aided by the Frederick K. Babson Fund of the Michael Reese Hospital and the Herbert L. Celler Fellowship Foundation, New York.

there occurred a complete reversal of the directions of the *Q–R–S* deflections of Leads I and III. This indicated that in bundle-branch block the position of the heart, as well as the site of the block determines the direction of the *Q–R–S* deflections.

The present investigation was made to discover if such changes could be demonstrated in man. In 6 individuals with so-called right bundle-branch block (older nomenclature) electrocardiograms were taken in various positions of the body and in different phases of respiration. Tracings were taken with the subject (*a*) lying on the back, (*b*) on the left side, (*c*) on the right side, (*d*) on the abdomen, (*e*) sitting up, (*f*) in deep inspiration and (*g*) in deep expiration.

Some degree of shift in the electrical axis appeared with change in position of the heart in every case. Twice, marked change in the electrical axis appeared. In these 2 cases, as shown in Figs. 1 and 2, a so-called right bundle-branch block (older terminology) became an indeterminate type. The change in the heart's position caused the *Q–R–S* deflection in Lead III to change from negative to positive, while in Lead I the *Q–R–S* deflection became smaller. The changes that occurred were not as marked as in the animal experiments since the degree of movement of the heart was more limited under the conditions of this investigation.

These results bear out the contention of Katz[2] that the direction of the *Q–R–S* deflection in the electrocardiogram in bundle-branch block is determined by the position of the heart as well as by the site of the block.

Krumbhaar,[3] Luten and Grove,[4] and Hyman and Parsonnet[5] have taken serial electrocardiograms which show the gradual development of bundle-branch block. We have seen similar records. Cases of right bundle-branch block (older terminology) were preceded by left axis deviation and a case of "left" bundle-branch block[5] was preceded by right axis deviation. This fact would support the original contention that the position of the heart—and this would include hypertrophy and dilatation—plays a rôle in the electrocardiographic configuration of bundle-branch block. This interpretation may serve to explain the apparent discrepancies between clinical and necropsy findings in certain cases of bundle-branch block.

Summary and Conclusion. 1. In 2 cases of so-called right bundle-branch block (older nomenclature), shift in the position of the heart changed the electrocardiogram to the indeterminate type of bundle-branch block.

2. The position of the heart as well as the site of the blocked bundle-branch determine the direction of the *Q–R–S* in the electrocardiogram of bundle-branch block. This may be the explanation of certain apparent contradictions in the findings of previous students of bundle-branch block.

3. It is suggested that electrocardiograms heretofore interpreted as left and right bundle-branch block be reported simply as intra-

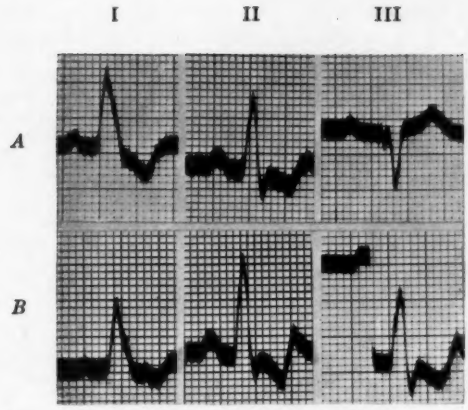

FIG. 1.—Case 2. *A*, Electrocardiogram taken with patient on back; *B*, lying on left side.

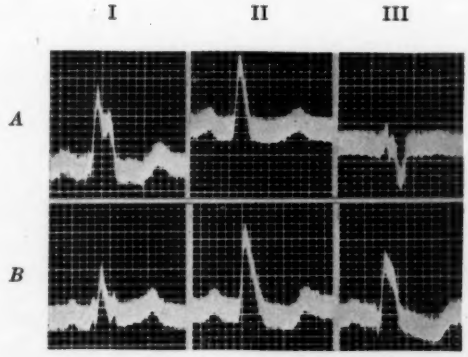

FIG. 2.—Case 6. *A*, Electrocardiogram taken with patient sitting; *B*, lying on left side.

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ventricular block of "bundle-branch block configuration" and that no attempt be made to locate the blocked bundle-branch from the electrocardiographic appearance alone.

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REVIEWS.

INTERNAL MEDICINE. ITS THEORY AND PRACTICE. By various contributors. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Pp. 1316; 37 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $10.00.

To quote from the preface: "The ever increasing complexities of internal medicine and the steadily mounting mass of facts that pertain to disease make it an impossibility for any one man to write with authority on such a large subject." This is the second one-volume textbook written by numerous contributors that has appeared in recent years. The advantage of such a book from the standpoint of factual excellence in all its sections is obvious. The editor of such a volume is, however, confronted with the necessity of avoiding certain pitfalls and difficulties. The larger the number of contributors, the greater is the task of proper coördination, of proper emphasis as determined by space assigned to various subjects, of avoidance of duplication. Again, not every medical author combines with his knowledge of the subject the facile vivid expression of an Osler, a Strümpell or a Dieulafoy. The editor is to be congratulated on his happy solution of these problems. The 27 writers who have contributed to this volume all hold professorial appointments in medical schools and as teachers are experienced in imparting their information to students. Worthy of comment is the inclusion of an excellent chapter on mental disorders. This volume will take its place as a standard text in American medical literature. R. K.

VARICOSE VEINS AND HEMORRHOIDS. By V. MEISEN, M.D., former Chief Surgeon to the Policlinic, Sundby Hospital, Copenhagen. With a Preface by AUG. KROGH, PH.D. Pp. 149; 25 illustrations, 8 colored plates. Copenhagen: Levin & Munksgaard, 1932; London: Oxford University Press, 1932.

THIS is an attempt to cover the entire field of injection of sclerosing agents to benefit varicose veins, hemorrhoids, varicocele, hydrocele and venous angioma.

In the section on varicose veins of the leg, the chapters on the anatomy and physiology are well done. Much space has been properly given to the consideration of deep vein phlebitis and postphlebitis sequelæ and complications. The various contraindications to both the injection and operative treatments are scantily treated, while treatment following deep vein phlebitis is somewhat rashly advocated. The technique is clearly given and follows closely the accepted methods. One is disappointed that more has not been given on recurrences, canalization of the thrombosis, newly formed veins and those cases that resist all sclerosing agents—questions that are now particularly engaging the thought of surgeons.

The injection of varicocele will meet with little enthusiasm and few

surgeons have anxiously awaited a new substance with which to inject hydrocele.

In the section devoted to hemorrhoids the general similarity between varicose veins of the leg and of the rectum is overemphasized, overlooking the important differences in the anatomy of the veins and the course of the circulating blood in varicose veins of the leg and of the rectum. For instance, in varicose veins of the leg it is pointed out that the direction of flow of the blood is downward to the deep veins through the communicating ones which are smaller and, therefore, the possibility of an embolus passing into the general venous circulation remote. This is not the arrangement in the rectum, however, and, the flow being from the smaller to increasingly larger veins, the greater chance of embolism is apparent.

Infection of most hemorrhoids was pointed out, but though fatal cases have been reported, the unsound practice of injecting into an infected area a highly irritating solution devitalizing to the tissues is recommended.

In referring to the surgical treatment of hemorrhoids, the author has denounced the clamp and cautery method because of the resulting stenosis and ectropion of the mucosa. However, stenosis of the rectum should not occur if the clamp is applied in the direction of the long axis of the rectum rather than on the circumference. Recurrences of hemorrhoids after the injection treatment has not been discussed.

In the hands of the general practitioner and inexperienced surgeon the book would give the unsupported and unwarranted view that the injection treatment of varicose veins of the leg and hemorrhoids had satisfactorily supplanted the surgical treatment of both these conditions and that shortly it might be equally well applied in the treatment of varicocele, venous angioma and varicocele. S. W.

Un Pericolo Sociale: Le Brucellosi. By Prof. A. Alessandrini and M. Pacelli, M.D., with a Preface by Prof. A. Ilvento, Vice-Director General of the Public Health Service. Pp. 184; 10 illustrations. Rome: Edizioni "Annali d'igiene," 1932.

Except for their failure to refer to Keefer's first report of proved human infection by the organism of contagious abortion of cattle, and the early work of American clinicians in delineating this phase of the disease, the authors have given a detailed presentation of the problem of Brucella infections, a problem which by the Section on Hygiene, League of Nations, was designated as "one of the most important world problems of public health." There are chapters dealing with the prevalence of brucelliasis in man and animals in the various countries; the bacteriology of Brucella; the sources of contagion; prophylactic measures against brucelliasis in the commonly affected domestic animals and in man; milk in relation to undulant fever. Complete from the Italian point of view, this monograph is, as far as the Reviewer knows, the most comprehensive in any language on the public health aspects of this subject. R. K.

Sane Sex Life and Sane Sex Living. By H. W. Long, M.D. With a Special Introduction by Dr. W. F. Robie. Pp. 151. New York: Eugenics Publishing Company, Inc., 1922. Price, $2.

A book which aims to "improve health, prolong life and promote virtue" by giving in non-technical language details of sexual life. Necessarily sold only to medical men, it is written for the laymen and much space

given to exhortation. Restricted to the right sort of reader, it doubtless would have its uses, though occasional strange bits of physiology are included. How to prevent the book from falling into the wrong hands is a problem that apparently does not concern author or introducer.

E. K.

FILTERABLE VIRUS DISEASES IN MAN. By JOSEPH FINE, M.D., B.Sc., D.P.H. (GLAS.), D.T.M. (LIVERP.), Assistant to the Professor of Public Health, Edinburgh University; formerly Research Assistant, Sir Alfred L. Jones Laboratory (Liverpool School of Tropical Medicine), Freetown, Sierra Leone; late Assistant Pathologist, Ancoats Hospital, Manchester. Pp. 144. Baltimore: William Wood & Co., 1932. Price, $2.25.

THE status of filterable virus diseases today is much the same as was the status of bacteriology about forty years ago: Our knowledge is so rapidly expanding that only the specialist can hope to keep even reasonably well informed. It is, therefore, desirable to have at not too infrequent intervals summaries and critical reviews of the important subject. This appears to be the object of the little book by Fine. It is well written, and it contains in compact form the essential parts of virus diseases in man. Moreover, it makes available in a single volume the recent advances in our knowledge. The references given at the end of each chapter, while not an exhaustive list of the literature, are a good guide for those who wish to become better acquainted with a fascinating field of pathology and clinical medicine.

The author's attempt to classify and systematize the virus diseases of man is helpful to the non-specialist. We wish to recommend this very readable book to all who would gain at least some acquaintance with a rapidly progressing part of medicine.

B. L.

FUNCTIONAL DISORDERS OF THE GASTRO-INTESTINAL TRACT. By WILLIAM GERRY MORGAN, M.D., F.A.C.P., Professor of Gastroenterology, Georgetown University Medical School, etc. Pp. 259; 32 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, $5.00.

ONE of the volumes of the Everyday Practice Series, under the editorship of Dr. Harlow Brooks, this book deals with the diagnosis and treatment of the various abnormalities of function of the digestive tract. The viewpoint is conventional and the presentation is conservative. There are numerous illustrative case reports.

R. K.

THE ACTION OF THE LIVING CELL: EXPERIMENTAL RESEARCHES IN BIOLOGY. By FENTON B. TURCK. Pp. 308; 17 illustrations. New York: The Macmillan Company, 1933. Price, $3.50.

SOME years ago the author, who died last November, isolated a substance which he named *cytost*. This he regarded as a cellular toxin which, being suddenly liberated in large quantities by injured tissues, caused shock and death. Not only did he recognize that the composition of cytost "is a biochemical problem which still awaits solution," but unfortunately so many of his views remained highly speculative theories and of his observations remained insufficiently controlled that they have not carried great weight

with students of the subject. Like Finley's views on the relation of the mosquito to yellow fever, or many of Sajous' theories of endocrine action, they remain as perhaps brilliant flashes of intellect which very rarely are of any value in substantially advancing biological science. The material accumulated in the book under the review in the opinion of the Reviewer only partly obviates this criticism. E. K.

El Asma Y Otras Enfermedades Alérgicas. By Dr. Carlos Jiménez Diaz. Pp. 945; 88 illustrations, some colored. Madrid: Editorial España, 1932. Price, 60 pesetas.

An unusually complete and well-balanced presentation of the subject and by all odds the best European text on allergic disorders that has come to our attention. The first third of the book deals with the theory, mechanism and etiology of allergy. Then follow 60 pages on the general symptomatology and diagnosis of allergic states. The rest of the volume deals with the various clinical manifestations of allergy, half the space being devoted to the allergic diseases of the respiratory tract, and the other half to allergic skin disorders, angioneurotic edema, migraine, and allergy in the digestive tract and elsewhere. It is in the field of digestive allergy that the author has made original contributions. Minor criticism: the lack of an index. There is a very extensive bibliography, thoroughly representative of the medical literature of the world. The book should prove most useful to all physicians who read Spanish. R. K.

Clinical Interpretation of Laboratory Reports. By Albert S. Welch, A.B., M.D., Clinical Instructor in Medicine in the University of Kansas School of Medicine in Kansas City, Kansas, etc. Pp. 366; 16 illustrations, 1 in color. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, $4.00.

The ever increasing use of laboratory procedures in the diagnosis of disease confronts the practitioner with the growing necessity of interpreting and evaluating the reports he receives from the laboratory. He will find a conservative and accurate guide in this book, the author of which is both clinician and pathologist. R. K.

The Nervous Child at School. By Hector Charles Cameron, M.A., M.D. (Cantab.), F.R.C.P. (Lond.), Physician in Charge of Children's Department, Guy's Hospital. Pp. 160. New York: Oxford University Press, 1933. Price, $1.50.

The theme is largely fatigue, expressing itself chiefly as vomiting and bilious attacks, abdominal pains and sensations, persistent rise of temperature, fainting and cardiovascular disorders, attacks of unconsciousness and convulsions, and disorders of sleep. Continuing, disorders of conduct are considered, as persistent lying, stealing, playing truant and masturbation. Considerable assurance is shown and exception may be taken to this statement: "But there is no such thing as a child of high intelligence who, in point of morals only, is imbecile."

A criminal of high intellectual endowment, robust and a writer of note, began to read at three and a half years and entered upon a life of crime

at nine. He was in a reformatory, a county jail and a penitentiary. Once, when arrested, there were 29 charges against him. He said he was always kindly treated as a child, had attended a private school, a primary school and a college. At 21 he inherited $34,000, spent it in 3 years and later in life received help from many prominent persons, yet he showed no self-reproach. He stated to Reviewer: "There is a born criminal and I am one." When last seen, he was 48 years old and was debating whether to return to crime or accept matrimony from a woman of some means and culture.

N. Y.

LIGHT THERAPY. By FRANK HAMMOND KRUSEN, M.D., Director of the Department of Physical Medicine, Temple University School of Medicine, Philadelphia. Foreword by JOHN A. KOLMER, M.D., DR.P.H., D.SC., LL.D., Professor of Medicine, Temple University School of Medicine. Pp. 196; 33 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, $3.50.

A WELL written and illustrated monograph designed for the general practitioner. Light as a therapeutic agent and its manner of use are written of with clarity. What is not known concerning the subject is outlined; its therapeutic limitations are stressed; its proven values are detailed. The entire subject is treated authoritatively and without bias. The book is worth while.

G. W.

THE BIOCHEMISTRY OF MEDICINE. By A. T. CAMERON, M.A., D.Sc., F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital; and C. R. GILMOUR, M.D., C.M., F.R.C.P. (C.), Professor of Medicine and Clinical Medicine, University of Manitoba; Physician, Winnipeg General Hospital. Pp. 506; 31 illustrations. Baltimore: William Wood & Co., 1933. Price, $7.25 (temporary price, $5.50).

THIS volume is a useful addition to that field of publication—the application of biochemistry to clinical medicine—so brilliantly inaugurated by the *Quantitative Clinical Chemistry* of Peters and Van Slyke. The authors, realizing the limitations of their shorter work, constantly refer to the American treatise, which seems destined for many years to serve as a model. The Reviewer agrees with the authors that *The Biochemistry of Medicine* may have a distinct field of usefulness for the less advanced "student of medicine receiving clinical instruction . . . and for the physician who received no special instruction in the medical applications of biochemistry."

The book deals adequately with such topics as glycosuria, sugar tolerance curves, the biochemistry of diabetes, anomalies of metabolism, anemias, edema, and renal, gastric and liver functional tests. Each chapter is followed by a moderately extensive bibliography and short summary.

A short work must of necessity suffer somewhat from arbitrary discussions, and a first edition often suffers from errors of omission as well as commission. The following is, therefore, offered in the spirit of looking forward to an improved second edition: (1) In the discussion of adrenalin hyperglycemia, no account is taken of the phenomenon of preferential burning of fat. (2) *In vivo*, during exercise, the respiratory quotient is but rarely 1, as the authors assume. Furthermore, it is erroneous to state "during muscular exercise the chief oxidation in the organism is that of lactic acid of muscle." (3) It would appear in a book of this type far less

important to discuss heptosuria, which has never been proved adequately, than to discuss such topics as the influence of type of food fat upon type of fat produced in the body—a problem of some medical interest. (4) In the discussion of synthalin, the idea of its possible value is conveyed, whereas many publications stress rather the liver damage that this drug causes. (5) The data in the chapter on the metabolism of water might well, at present, be presented in osmolar terms. (6) The section on edema is relatively poor. Too much space is devoted to the theories of Fischer, none at all to the recent important work upon the relationship of serum proteins to edema. (7) "Conant and Scott have furnished proof that methemoglobin has only one-half of the removable oxygen of oxyhemoglobin. It (oxygen) is held more firmly than that in oxyhemoglobin, so that hemoglobin cannot function as an oxidation carrier." The authors have misquoted the work of Conant and Scott, and apparently have not realized that oxygen *per se* is not concerned with the oxidation of hemoglobin to methemoglobin.

In spite of these various suggestions, the Reviewer favorably recommends this short treatise to the intern and practitioner of medicine. D. D.

NOSOKOMEION. QUARTERLY HOSPITAL REVIEW. No. 2, APRIL, 1933. Containing the Proceedings of the Third Hospital Congress. Pp. 441. Stuttgart: W. Kohlhammer.

THIS number of the official organ of the International Hospital Association contains the reports and proposals of the Third International Hospital Congress recently held at Knocke Sur Mer, Belgium. For the convenience of all of its members it is printed in five languages. The work of its Study Committee, dealing as it does with the construction, equipment, administration, services and finances of hospitals throughout the civilized world, has as its far-reaching effect not only the dissemination of information concerning hospital practices but also a strong tendency toward standardization of procedures and techniques. Not only is this issue of the greatest practical value to those interested in hospitals because it summarizes world beliefs and practices, but it serves also to discourage the setting up of any climatic, racial or language boundaries in so far as they effect the principles and practice of caring for the sick. J. D.

SURGICAL ANATOMY. By C. LATIMER CALLANDER, A.B., M.D., F.A.C.S., Assistant Clinical Professor of Surgery and Topographic Anatomy, University of California Medical School; Associate Visiting Surgeon to the San Francisco Hospital. With a Foreword by DEAN LEWIS, M.D., Sc.D., LL.D., F.A.C.S. Pp. 1115; 1280 illustrations, some in colors. Philadelphia: W. B. Saunders Company, 1933. Price, $12.50.

THIS volume has, on the whole, been beautifully prepared and printed and fills a real need in the field of surgical anatomy. The many chapters cover the entire field of surgical anatomy. The author states that, with his father, "Recognizing accurate anatomic knowledge as the basis of surgical technique, we planned to present anatomic facts in terms of their clinical approaches, the paths of extension of pathologic processes, and the common operations. We worked together assembling and organizing material until three years ago when I was left to finish alone.

"This text is not a systematic treatise; it is intended to be explanatory

and utilitarian rather than encyclopedic. To avoid repetition of material, cross-referencing is used throughout. Most of the illustrations are original drawings of dissected material. If any of them are derived from sources not credited, the oversight is unintentional."

The illustrations are good; some, of course, would have been enhanced by the use of color. The anatomic data are well presented. Surgical technique is discussed briefly and the various operative steps are often illustrated. As Dr. Lewis says in the Foreword, the "book is printed with the definite idea of indicating the paths of surgical approach to the pathologic process which is to be removed or corrected."

While certain subjects are so familiar to the experienced surgeon that prolonged discussion may seem unnecessary, for the student and young surgeon these may be of first importance. From this point of view, the author has given too little space to the surgical anatomy of the appendix. There is, of course, the ever-present danger of attempting to cover so much ground that the book really becomes an abridged textbook of anatomy with added surgical implications. By way of further criticism from the student and clinical standpoint, it is better to discuss the anatomy from the viewpoint of the surgeon rather than the anatomist. The illustrations often have so many leads (Fig. 316 has 41) that the result is one of confusion rather than clarity.

This book should be well received and the author is to be congratulated on the work he has done. I. R.

ROENTGENOGRAPHIC STUDIES OF THE URINARY SYSTEM. By WILLIAM E. LOWER, M.D., F.A.C.S., Chief of Department of Urology, Cleveland Clinic; former Associate Professor of Genito-Urinary Surgery, Western Reserve University; Surgeon to Cleveland Clinic Hospital; and BERNARD H. NICHOLS, M.D., F.A.C.R., Chief of Department of Roentgenology, Cleveland Clinic. Pp. 812; 812 illustrations. St. Louis: The C. V. Mosby Company, 1933. Price, $16.

THIS is but the third book to appear in this country presenting the interpretative value of roentgenology in urology. It differs markedly from its predecessors in its format. Recognizing that the urologist has much to learn concerning the interpretation of roentgenograms, and that the roentgenologist has infinite need to become familiar with the depiction and recognition of urologic pathology and its surgical indications, this book devotes but 70 pages to technical methods and pathologic conditions, with a brief and interesting chapter on other lesions of the upper right quadrant; to be followed by 733 pages depicting the roentgenographic findings in 443 case studies. Each case is presented with a brief history, clinical findings, cystoscopic report, roentgenographic interpretation and surgical diagnosis. It is an atlas presenting the most complete exposition of the subject in all its phases. The plates are exquisitely reproduced and their interpretation aided by miniature-graphs that are unique and intrinsically valuable.

A. R.

INTRACRANIAL TUMORS. By PERCIVAL BAILEY, Professor of Surgery, University of Chicago. Pp. 475; 157 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $6.00.

In the Preface we read that "the time is past when discussions of intracranial tumors as a whole can longer be profitable. It is true that such tumors, if allowed to develop long enough, have this in common that they

give rise to intracranial hypertension. So may abdominal tumors cause enlargement of the belly, yet who would think of discussing fibroma of the uterus, carcinoma of the liver and ovarian cyst as though they were similar lesions?"

After a brief but excellent discussion of the problems of tumors in general, the cranial tumors in particular are discussed, their origins explained and the varieties classified. Following this comes an excellent description, well illustrated, of the anatomy and physiology of the parts concerned. The individual tumors are then taken up. For each there is a preliminary description of the appearance, gross and microscopic, of the seat of occurrence, the anatomical injuries effected, the physiologic disturbances that inevitably follow; and then a series of case studies emphasizing these points and bringing out so far as possible the diagnostic differential points of the tumor under consideration.

The text is excellent, entertaining and profitable and is illustrated by drawings that seem adequate for their purpose, though, as compared with the photomicrographs that might have been introduced but for the author's objection to glazed paper, they leave much to be desired.

Surgical treatment, regarded as of interest to the specialist only, is touched upon very sketchily, the purpose of the work being to enable the reader to understand the tumors, not operate upon them. J. McF.

PRÉCIS D'ANATOMIE PATHOLOGIQUE. In two volumes. By G. ROUSSY, R. LEROUX and CH. OBERLING. Pp. 1344; 582 illustrations. Paris: Masson et Cie, 1933.

ALL pathologists should know of this work of three of the best-known French pathologists. Americans have for a generation or more received their chief inspiration from German investigators and have, in consequence, become most familiar with their language and output. But one of the results of the World War was to bring about an interest in French literature and science, showing that another great people had been and is actively investigating and producing. This book is a striking example of their good work. In two volumes, conveniently small, with superb illustrations, mostly drawings, and a text brief and to the point, the subject is presented in every modern detail. J. McF.

HISTORY OF UROLOGY. In Two Volumes. Prepared under the auspices of the American Urological Association. Editorial Committee: EDGAR G. BALLENGER, WILLIAM A. FRONTZ, HOMER G. HAMER, BRANSFORD LEWIS, Chairman. Pp. 746; 49 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, $8, set.

THESE two authoritative and well-documented volumes make it difficult to realize that urology as a specialty had its start in the seventies and that even by 1902, when the American Urological Association was formed, specialists in this field were but few. The present work gives a comprehensive historical review of the development of urology, chiefly in America, with especial emphasis on the achievements of the Association which sponsored the preparation of the work. The plan adopted is to devote a chapter apiece to the Association, to New York, Philadelphia, Boston, Baltimore, Chicago, the Middle West and the West Coast, to be followed by 22 further chapters on various important urologic topics, all by different and well-known authors. In these chapters the subject has been followed

since ancient times, though necessarily the most space is devoted to modern developments. Especially interesting to the general reader is Dr. Caulk's 35-page chapter on Outstanding Contributions to Urology, which, pardonably enough, emphasizes the American contributions and again brings out the tremendous development of the subject during the present century. The work is well turned out and reasonably free from errors, though meagerly illustrated. Its chief defect—and a serious one—is the absence of an index, thus offsetting much of the value of its documentation.

E. K.

BOOKS RECEIVED.

NEW BOOKS.

Life in the Making. By DR. ALAN FRANK GUTTMACHER, Associate in Obstetrics, Johns Hopkins University; with the assistance of ELLERY RAND. Pp. 297; 8 illustrations. New York: The Viking Press, 1933. Price, $2.75.

The Surgical Clinics of North America, Vol. 13, No. 4 (Mayo Clinic Number, August, 1933). Pp. 215; 65 illustrations. Philadelphia: W. B. Saunders Company, 1933.

International Clinics, Vol. 3, Forty-third Series, September, 1933. By Various Contributors. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 316; illustrated. Philadelphia: J. B. Lippincott Company, 1933.

Paralysis in Children. By R. G. GORDON, M.D., D.Sc., F.R.C.P. (EDIN.), Physician, Bath and Wessex Orthopædic Hospital; Physician, Royal United Hospital, Bath, etc.; and M. FORRESTER BROWN, M.D., M.S. (LOND.), Surgeon, Bath and Wessex Orthopædic Hospital; Surgeon to County Orthopædic Clinics, Wiltshire, Somerset and Dorset. Pp. 328; 116 illustrations. New York: Oxford University Press, 1933. Price, $4.50.

The Diagnosis and Treatment of Diabetes. By W. WILSON INGRAM, M.C., M.D. (ABER.), Honorary Physician and Physician-in-Charge of the Clinic for Diabetes Mellitus, Royal North Shore Hospital, Sydney, etc.; and G. V. RUDD, M.Sc. (MELB.), Research Biochemist, Institute of Medical Research, Royal North Shore Hospital, Sydney. With a Preface by C. G. LAMBIE, M.C., M.D., F.R.C.P., F.R.S.E., Bosch Professor of Medicine, University of Sydney. Pp. 88; illustrated. Australia: Angus & Robertson, Ltd., 1933.

Clinical Science Incorporating Heart, Vol. I, No. 1. Edited by THOMAS LEWIS, M.D., F.R.S., aided in the selection of papers by T. R. ELLIOTT, M.D., F.R.S., R. T. GRANT, M.D., P. P. LAIDLAW, F.R.S., EDWARD MELLANBY, M.D., F.R.S., WILFRED TROTTER, M.S., F.R.S., and E. B. VERNEY, F.R.C.P. Pp. 158; illustrated. London: Shaw & Sons, Ltd., 1933. Price, 37/6.

Un Pericolo Sociale: Le Brucellosi. By PROF. A. ALESSANDRINI and M. PACELLI. M.D., with a preface by PROF. A. ILVENTO, Vice-Director General of the Public Health Service. Pp. 184; 10 illustrations. Rome: Edizioni "Annali d'igiene," 1932.

(For Review see page 725.)

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat.—A great deal of interest has been occasioned by the frequently confirmed observation that in certain types of Bright's disease and in certain conditions of undernourishment there is a well-marked hypoproteinemia. In the case of Bright's disease this is attributed to the loss of protein as albumin in the urine and in the states of undernutrition to a protein want from dietary inhibitions or insufficiency. At times it is conceded that both factors may play a part in the production of edema. BLOOMFIELD (*J. Exp. Med.*, 1933, **57**, 705) deems it advisable to analyze critically the mass of evidence for what he terms the loss and lack theory and to point out that there may be some other causative factors which play a part in this condition. He very fairly presents the arguments in favor of this protein loss and lack conception of the cause of edema. He then considers the published reports of those who are qualified and discusses their experiments. For example, he states that in Leiter's experiments the withdrawal of plasma was excessive and is not likely to be paralleled in man. In Whipple's experiments the dogs built up their protein to normal level even after fasting for a period of 2 weeks. Protein loss, he concedes, may lower blood proteins, but it must be excessive. In case of the observations of Peters and others he feels that it is quite possible that there was an actual disturbance of the protein-building mechanism to explain the hypoproteinemia. In conjunction with Bright's disease, the protein urinary loss should bear some direct relationship to blood proteins. It should be expected that these should be termed normal or a higher level if large quantities of protein were given by mouth. Even in extremely heavy proteinuria, plasma proteins in some instances were moderately low, whereas others with less extreme proteinuria had under 4 grams per cent. Even more striking are the experiments of Peters and Bulger, who fed high-protein diets to nephritics with low blood proteins. Irrespective of the diet and the loss or storing of nitrogen, blood proteins remained at a fairly constant level, indicating that the low blood protein was not related to nitrogen metabolism of the body as a whole, but rather to some special failure of the blood protein

mechanism, possibly exaggerated by the proteinuria. Again, it is possible to find low blood proteins in well-nourished individuals who have not suffered from a protein dietary deficiency. In order further to substantiate his ideas, a series of experiments were carried out by Bloomfield with mature rats. They were given an experimental diet without carrots but adequate in calories, salts and vitamins and with a minimum of protein. The serum proteins of these animals were examined *en masse* after prolonged dietary observation, during which time the animals remained entirely well. In the first initial period there was a fall in the concentration of serum proteins of approximately 10 per cent at the expense of serum albumin. Upon a return to a diet with adequate protein there was an equally prompt restoration to the initial serum protein level. These fluctuations are very rapid and so slight it is presumed they are physiologic rather than pathologic. There was no further drop of significance during a period of 20 weeks, corresponding to a period of 10 years of human life. In the killed rats who were sacrificed on the 147th day the albumin-globulin ratio was within normal range. In a group of rats, at the end of the 20-week period, placed on a control diet with casein 16 per cent, the serum protein rose very promptly. On a starvation diet there was an initial drop but no further significant changes. The results of these experiments did not accord with those of many others. Bloomfield suggests that the subject needs further study and the exact nature of the mechanism requires special analysis. There may be other possible etiologic factors, such as vitamin deficiency, excess of certain foods, such as carrots, insufficient caloric intake, and infection, to be considered.

SURGERY

UNDER THE CHARGE OF
I. S. RAVDIN, B.S., M.D.,
J. WILLIAM WHITE PROFESSOR OF SURGICAL RESEARCH, UNIVERSITY OF PENNSYLVANIA,
AND
C. G. JOHNSTON, M.S., M.D.,
INSTRUCTOR IN SURGERY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

Larvæ Therapy.—Numerous references are to be found in the literature of ancient, medieval and modern medicine concerning the beneficial results from the introduction of maggots in various types of wounds. Flies have deposited their eggs and larvæ have developed in poorly cared for wounds of men and animals since the dawn of history, and it is not surprising that the effects of fly larvæ on wounds have been frequently described. It is surprising, however, that the descriptions of PARÉ (*Les Œuvres d'Ambroise Paré*, ed 2, p. 1576; ed. 11, A. Lyon; Pierre Rigaud, 1652; translation from the Latin by Theodore Johnson, London, Clark, vol. **10**, p. 249; vol. **11**, pp. 277, 1678; *Selections from the Works of Ambroise Paré*, by Singer, 1924, p. 218) and LARREY (*Observations on Wounds, and Their Complications by Erysipelas, Gangrene and Tetanus, etc.*, translated from the French by E. F.

Rivinus, Philadelphia, Key, Mielke and Biddle, 1832, p. 34; *Clinique Chirurgicale*, Paris, 1929, pp. 51, 52) and the occasional later references to the effect of maggots were largely ignored until BAER (*Proc. Inter-State Post-Grad. Med. Assn. of North America*, Detroit, 1929, p. 370) introduced maggot therapy as a major part of the treatment of osteomyelitis in 1929.

GOLDSTEIN (*J. Bone and Joint Surg.*, 1931, **13**, 476) has reviewed the literature of maggot therapy previous to Baer's publication. While an occasional observer had recognized that a wound which had become contaminated with maggots was possibly benefited by their presence, most clinicians have felt that a wound containing maggots was detrimental as well as repulsive to the patient and indicated poor wound care.

BAER'S (*J. Bone and Joint Surg.*, 1931, **13**, 438) results indicated in a striking manner that larvæ of the blow-fly aided in the healing of cases of osteomyelitis. The lesions which he reported healed more rapidly than if surgery alone had been resorted to, appeared cleaner and the granulation tissue looked healthier. Baer did not account entirely for the beneficial results of this type of therapy. He felt, however, that the maggots ate the necrotic tissue and caused changes in the hydrogen-ion concentration of the fluid in the wound which was beneficial to wound healing. His description of the action of the maggots intimated that the maggots have an instinct for cleaning wounds and that they ate ravenously to remove all necrotic material and to loosen sequestra.

MARTIN and HEEKS (*Ann. Surg.*, 1932, **96**, 930) point out that on the basis of the entomological studies of FABRE (*Souvenirs Entomologiques* [*Dixieme Serie*] *La Mouche Bleue de la Viande-Le Ver*, p. 259; Laponte, p. 241) maggots are not true scavengers in that they cannot subsist on solid food but must live on a liquid diet. In addition, these authors felt that Baer's results did not indicate that larval therapy has any advantages over the Orr method of treatment of osteomyelitis.

Since Baer's original paper many reports have appeared which substantiate Baer's contention that maggot therapy is an efficacious method for the treatment of osteomyelitis. The manner by which these results are brought about is, however, not so well understood. Naturally the most plausible explanation is that the maggots act as scavengers, eating bacteria and tissues that have become necrotic and soft. WEIL, SIMON and SWEADNER (*Am. J. Surg.*, 1933, **19**, 36) reported that in addition to a scavenger effect the larvæ produce an excretory proteolytic substance which hastens liquefaction. LIVINGSTON and PRINCE (*J. Am. Med. Assn.*, 1932, **98**, 1143) state that the effects are due to an active principle which they are able to extract from the dead bodies of maggots. These authors treated 100 cases of primary osteomyelitis, infected wounds, and infected compound fractures with maggot extract and polyvalent vaccines, and obtained healing in 88 per cent of their patients. They concluded that beneficial results were due to the maggot extract and not to the vaccine, since the vaccine alone proved ineffectual. ROBINSON and NORWOOD (*J. Bone and Joint Surg.*, 1933, **15**, 409) are of the opinion that live maggots are necessary, since macerated maggots show no bacteriocidal properties when added to cultures. These authors point out that maggots ingest large numbers of bacteria,

bacteria being found in large numbers in the foregut while there is apparently a disappearance of organisms in the lower intestinal tract. In addition they express the view that favorable action due to maggots results from the ability of the larvæ to reach small recesses of the wound, removing bacteria and débris, and to a stimulating action which causes a thin serous discharge. This discharge assists in washing out large numbers of bacteria and assists in drainage of the wound.

To those who have witnessed the results brought about by the introduction of maggots in osteomyelitis, this form of treatment appears promising. The results reported thus far indicate that this method is on a sound basis. Whether the Orr treatment or the Baer treatment is the method of choice will depend largely on further study, since too short a time has elapsed to draw definite conclusions.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

The Presence of Estrogenic Substances in Bituminous Material.—Inasmuch as bitumen is known to be composed in part of fixed residues of fossilized animal life, and since estrogenic material has also been demonstrated in both the lower forms of animal life and plant cells, ASCHHEIM and HOHLWEG (*Deutsch. med. Wchnschr.*, 1933, **59**, 12) studied a group of extracts obtained from various types of bituminous material by means of the several recognized biologic tests and found them to contain variable but significant amounts of estrus hormone. The extracts studied were derived from mineral oil, peat, soft coal and asphalt. These materials were demonstrated to contain from 400 to 10,000 mouse units per kg. of the native substance. Positive reactions were obtained by means of the Allen test, action on the uterus of castrated animals, on the mammary gland, on the cervical ganglion cells and upon the anterior lobe of the hypophysis. The significance of these findings for therapeutics is for the present left without comment by the authors.

A New Preparation Inhibiting Thyroid Activity in Grave's Disease.—About 2 years ago Blum demonstrated the existence of a substance in blood, apparently of hormonal nature, which possessed marked antithyroid activity. This property was demonstrable in biologic experiments as well as clinically by the use of large quantities of whole blood or even of preserved dried blood but proved objectionable and impracticable for clinical use. Further researches have lead to the preparation

of a highly purified extract of blood, called tyronorman. This preparation is standardized biologically, 1 unit being capable of neutralizing the activity of $\frac{1}{1000}$ mg. of iodin in the thyroid gland and it is further standardized biologically with reference to its power to reduce the basal metabolism in rabbits when raised by the administration of thyroid. The preparation is available in tablets containing 10 units per tablet. HERZFELD and FRIEDER (*Deutsch. med. Wchnschr.*, 1933, **59**, 84) report upon the use of this preparation in 18 cases of Graves' disease selected from among those of extreme severity and in whom the usual operative procedures were felt to be too dangerous. They administered daily doses, ranging from 30 to 90 units, and observed a marked improvement in all but 2 of the patients. The improvement was rarely noticed until the second week of treatment but was usually rather prolonged, although subsequent administration of smaller doses were frequently necessary. The patients showed a reduction in heart rate, a progressive and marked fall in basal metabolism, a pronounced increase in weight and a rapid disappearance of the symptoms referable to the vegetative nervous system. Exophthalmos was also generally diminished, but the enlargement of the thyroid gland was not materially influenced. One of the two failures occurred in a patient whose condition was complicated by a tumor, the other in a patient who was not coöperative in carrying out the treatment. Although the treatment alone was fairly effective, it was found that the results of the administration of tyronorman were improved if the patient followed the restrictions in diet originally advocated by Blum, namely, the avoidance of all animal food and its derivatives of protein nature, of coffee, tea, nicotin and alcohol, limiting the diet thereby chiefly to fat and carbohydrates along with vegetables, fruits and an abundance of milk.

The Circulatory Actions of Commercial Liver Preparation.—KRAYER (*Deutsch. Med. Wchnschr.*, 1933, **59**, 576) reports a series of pharmacologic studies on the circulatory actions of four well-known commercial preparations of liver used for the control of anemia, and contrasts them with the similar actions of a preparation known commercially as eutonon, which is a liver preparation reputed to have pronounced circulatory actions. The results of his experiments are striking in that they failed to reveal any significant circulatory action of eutonon on the heart-lung preparation while all of the other liver extracts exerted identical and marked effects. The actions observed were a pronounced increase in coronary blood flow, a marked stimulation of cardiac rate and a more or less significant reduction in the minute volume output of the heart. Despite the observations of these actions on the heart-lung preparation, the author emphasizes the fact that there is no pharmacologic reason for believing that any of these preparations may be regarded as therapeutically valuable in the treatment of any of the forms of cardiovascular disease.

Clinical Observation of the Reaction of Lecithin on Refractory Cases of Cardiac Failure. — Led by pharmacologic and physiologic experiments of other workers who showed the beneficial effects of the administration of lecithin in the restoration of the loss of phosphatids and cal-

cium from the exhausted heart, SCHEFF (*Zeitsch. f. Kreislauf.*, 1933, **25**, 285) studied 5 patients intensively over a considerable period of time. His observations showed that the parenteral administration of fairly large doses of lecithin was invariably followed by a marked improvement in the efficiency of the heart and a restoration of its ability to respond to the administration of the usual cardiac stimulants, to which it had apparently become unresponsive. This effect of lecithin was further controlled by a fairly prompt return of cardiac inefficiency and loss of responsiveness when its administration was omitted. The author does not contend that lecithin itself is a cardiac stimulant but rather that it restores the physiologic state of the heart, thus permitting it again to respond to appropriate drug therapy.

PEDIATRICS

UNDER THE CHARGE OF

ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Poliomyelitis: Comparison Between the Epidemic Peak and the Harvest Peak.—TOOMEY and AUGUST (*Am. J. Dis. Child.*, 1933, **46**, 262) call attention to the synchronism between the peak of the epidemics of poliomyelitis and the peak of the harvest in an attempt to explain at least one method of transmission. They state that infantile paralysis need not be due necessarily to fruits and the like, but perishable foods might serve as one of the vehicles by which the disease is carried. Such a conception would explain the somewhat explosive and dispersive type of infection that occurs during the harvest peak. They feel that Aycock's "southern incidence curve" could be explained on the basis of an earlier harvesting date. The latter observer called attention to the fact that the incidence of this disease bears a resemblance to the incidence of typhoid fever. Kling called attention to its resemblance to dysentery. Its coincidence with gastro-intestinal disease is very apparent if one constructs a dysentery percentage curve from figures found in the Japanese Sanitary District report of 1929, with its peak in August and September. It can be seen that there is an obvious similarity between the curves of the incidences of poliomyelitis and dysentery. The typhoid curve of the same district was plotted, and confirmed Aycock's epidemiologic observations. Flies are a common carrier of typhoid and dysentery. Johnson detailed the number of flies that were caught weekly in various places in New York City. The elements of chance entered a great deal in this consideration, but when the figures were arranged and a curve plotted, it is interesting to note that the curve of the greatest number of flies occurred a little before the season of the greatest incidence of the disease. The handling of infected fruit or vegetables by infected people, the eating of infected fruits and vegetables by cattle with subsequent infection of milk, and the spreading of the infection from fruit to fruit by flies could serve to explain the spread of the disease and the incidence at this time of the year. To

this should be added Kling's claim of water as a possible source of infection. The curves plotted by the authors showed that the incidence curves of the disease followed closely the curves of the harvest of the perishable foods. The curves for other countries, while inferential approximations, bore a striking similarity to these curves. While they do not draw definite conclusions they remark on the fact that in their locality the peak of the poliomyelitic incidence curve should correspond so closely to that of the harvesting curve.

Preventing Loss of Weight in the Newborn.—KUGLEMASS, BERGGREN and CUMMINGS (*Am. J. Dis. Child.*, 1933, **46**, 280) say that loss of weight in the newborn is sanctioned universally, but they claim that this is without physiologic foundation. They claim also that the newborn infant is markedly underdeveloped for the long duration of human gestation, and so requires continuous supervision for the prevention of potential pathologic changes. They observe that the neonatal growth gradient continues unaltered during the postnatal period according to the analysis of the transitional growth trends of the body as a whole as well as of its tissues and organs. Therefore they conclude that the initial loss in weight is necessarily extrinsic. Postnatal loss of weight does not occur in animals of any size, gestation period or scale in evolution, according to a survey of observations of veterinarians and others in contact with animals. The authors state that the initial loss of weight in the human newborn is the result of dehydration and semi-starvation, which conditions are unfavorable for the nutritional, physical and environmental adjustments besetting the newborn. The therapeutic procedures in the past for decreasing the loss of weight in the newborn were not successful because they were not based on the physiologic needs of the newborn, disturbed by the shock of birth. The initial loss in weight in the newborn can be prevented by the administration of a solution consisting of 6 per cent gelatin, 3 per cent dextrose and 0.5 per cent sodium chlorid at 2-hour intervals throughout the 24-hour period immediately after birth. The gelatin hydrates the blood and tissues, and it raises body heat by virtue of its specific dynamic action, and it reduces the clotting time of the blood. Dextrose brings the hypoglycemia of the newborn to normal. Sodium chlorid raises the initially low blood chlorid and favors hydration. The average loss of weight in newborn infants receiving the hydrating solution was 1.7 per cent as the irreducible minimum as compared with the average loss of 7 per cent in the controls. The characteristic clinical picture of the newborn is a result of birth shock, and is more effectively combated by the hydrating solution than by milk mixtures during the first 2 or 3 days of life. It was found that the total fluid intake of newborn infants properly conditioned to both bottle and breast was as much as twice that of the group receiving the routine nursery care. The method of preventing loss of weight in the newborn produces, in addition, the rapid disappearance of the so-called physiologic apathy, somnolence and stupor secondary to birth shock and the compensated acidosis universally present.

Endemic Cerebrospinal Fever in Childhood.—SHAW and THELANDER (*J. Am. Med. Assn.*, 1933, **101**, 746) state that the progress of these

cases through the varying stages of infection presents many interesting possibilities for speculation regarding the pathologic physiology. The evidence is fairly conclusive that the entrance into the body is by the way of the respiratory tract. This is followed by an infestation of the blood stream scarcely equaled by any other bacterial infection, which in turn is followed by localization of the organism in the skin and in serous membranes of the body. The original focus of infection is usually of a minor nature, although sometimes it is grossly apparent. Actual empyema of the antrums of the ethmoid sinuses is described, but is not the rule. These observers have not seen nor found described such local changes in the bloodvessels, thrombosis or phlebitis of larger veins from which dissemination of infected emboli might result in the usual manner of producing a sepsis. Neither are secondary disseminating foci, such as heart valve lesions, the rule. When organisms are seen free in blood smears, they are found within cells or free in the plasma, and do not appear in bacterial clumps nor enmeshed in fibrin. The areas of skin localization present significant information. The marked skin eruptions tend spontaneously to regress, and following intravenous treatment they quickly and almost entirely disappear. This is not reconcilable with an embolic theory or with any mode of origin other than their production by a vascular toxin, which may be neutralized by an antitoxic effect of the serum. In meningeal localization, areas of perivascular inflammation first appear which are not unlike the early changes in the skin. Slight signs and symptoms of meningeal irritation sometimes accompanied the stage of sepsis even when meningitis did not develop. The original meningeal reaction is in the nature of a meningismus dependent on vascular changes rather than a response to bacterial infection of the spinal fluid. The evidence seems fairly convincing that the manner in which the organism gains unimpeded entrance to the blood, and thereafter affects distant tissues, depends on the action of an exotoxin or endotoxin which produces vascular changes of such a nature as to permit this massive ingress from a small original focus and in a similar manner permits egress to the tissues.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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The Rôle of the Streptococcus in Trichomonas Vaginitis.—So much has been written in recent years about the type of vaginitis in which the Trichomonas vaginalis is supposed to be the etiological factor that the contribution of HIBBERT (*Am. J. Obst. and Gynec.*, 1933, **25**, 465) is of interest. He states that the Trichomonas vaginalis may be found in

the vaginal secretions of many women for long periods of time without producing an acute vaginitis. On the other hand, in a large percentage of cases having an acute vaginitis where the Trichomonas vaginalis exists, there is an associated predominant growth of a Gram-positive, non-hemolytic, short chain streptococcus present which is capable of producing an active vaginitis when not associated with the Trichomonas. He has found that by repeated vaginal application of a specific streptococcic bouillon filtrate the active growth of the organisms in the vagina ceases and the vaginitis subsides in spite of the persistence of the protozoön in the secretions. After describing the method of preparing the bouillon filtrate he states that the method of treatment of the patients was uniform. All other methods of treatment were suspended, all douches forbidden and the patient was allowed only one tub bath daily. In indicated cases repeated cauterization of the cervix was resorted to where cervicitis was present. The vaginal canal was dried with sterile cotton pledgets and a large cotton tampon, saturated with the bouillon filtrate, was packed against the cervix and allowed to remain in place for 12 hours, during which time the patient was advised to remain off her feet in order to aid in retaining the fluid in the vagina. The treatment was repeated 2 or 3 times a week until the vaginitis disappeared.

Relationship Between Ovarian Follicle Cysts, Hyperplasia and Uterine Myomata.—Although myomatous tumors of the uterus are the most common neoplasms of the female generative organs, their exact etiology remains unknown. After discussing the various theories pertaining to the histogenesis and etiology of these tumors, WITHERSPOON (*Surg. Gynec. and Obst.*, 1933, **56**, 1026) presents evidence to show that the unopposed action of estrin (the ovarian follicular hormone) in the absence of corpus luteum influence is the cause of hyperplasia of the endometrium. Furthermore, he suggests that the unopposed action of estrin on the myometrium, if prolonged sufficiently, would result in fibromyomatous growths. This hypothesis is based on a study of 26 cases of hyperplasia of the endometrium, in which operation was done and the diagnosis as such was made from microscopic study and in which a second operation was performed for fibroids after an approximate interval of 4 years and 4 months, and also upon a study of 124 cases of fibroids, diagnosed microscopically. In this latter group the associated ovarian and endometrial findings present evidence which he believes adds support to a cause and effect relationship between ovarian follicular cystic formation, hyperplasia of the endometrium and fibromyomata of the uterus. Therefore, he advances an hypothetical conclusion that the unopposed action of estrin on the uterus results in immediate endometrial changes characterized by hyperplasia, and, secondly, in more latent myometrial changes in the nature of fibromatous growths. It is now believed by many observers that functional uterine hemorrhage which is dependent upon endometrial hyperplasia can be controlled by the use of anterior pituitary hormone which counteracts the effect of the ovarian follicular fluid. Reasoning by analogy, if this theory of Witherspoon be valid, the prophylactic use of anterior pituitary hormone should decrease the incidence of uterine fibroids.

OPHTHALMOLOGY

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The Fundus in Hypertensive Disease and Its Sequels.—SCHEERER (*Med. Klin.*, 1933, **29**, 245) thinks that the initial stage in so-called "blood pressure disease" is the "spastic-atonic symptom complex of vasoneurosis" in which the arterial capillaries are narrowed and the venous dilated. When the spastic narrowing involves the arterioles also, the blood pressure rises. In either of these two stages closure of the central artery or vein of the retina can occur without the presence of organic changes. A continuance of the spastic narrowing leads to organic changes in the retinal arterioles and, if nephrosclerosis occurs also, the terminal picture of albuminuric retinitis may be seen. The characteristic retinal change in this primary type of hypertension is contraction of the arteries with relative dilatation of the veins. In nephrogenic hypertension, by contrast, the retinal veins are narrowed as well as the arteries. Albuminuric retinitis may be the terminal picture in this type of hypertension also. Arterial and venous closures do not occur. In the senile type of arteriosclerosis without rise of blood pressure, narrowing of the retinal arteries and veins occurs with disappearance of many of the smaller vessels, obliteration of capillary beds, and thinning of the retina. In this type, arteriosclerotic closure of the central artery or vein may occur and senile macular degeneration is frequent.

On Changes of the Optic Canals in Cases of Intracranial Tumor.—LYSHOLM and OLIVECRONA (*Acta chir. Scand.*, 1932, **72**, 197) studied the roentgenograms of the optic canals in their cases of tumors in the chiasmal region with special reference to their aid in making a differential diagnosis of the type of tumor present. Changes in the optic canals were observed in gliomas of the optic chiasm, pituitary adenomas, and cholesteatomas of the suprasellar region. The changes present in association with gliomas of the optic chiasm and with suprasellar cholesteatomas were quite similar and consisted of dilatation of one or both optic canals with enlargement of the sulcus chiasmatis but without destruction of the walls of the canals. In 2 cases of chromophobe adenoma of the pituitary, in addition to dilatation of the optic canals, considerable destruction of the walls of the canals was present in association with rather extensive changes in the sella. A marked unilateral dilatation of the optic canal was observed in a case of tumor of the intraorbital portion of the optic nerve. It is suggested that a more routine study of the optic canals in chiasmal lesions may bring out further differential diagnostic points.

OTO-RHINO-LARYNGOLOGY

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Effects of Radiation on Allergic Nasal Mucosa.—Inasmuch as the therapeutic results of vasomotor (hyperesthetic) rhinitis by medical, surgical and allergic methods have been frequently disappointing, a consideration of the known effects of radiation on normal and pathologic nasal mucosæ suggested to BERNHEIMER and CUTLER (*Arch. Otolaryngol.*, 1932, **16**, 561) the use of radium to correct the local pathologic processes encountered in allergic nasal conditions. Accordingly, 40 patients with hyperesthetic rhinitis were irradiated—all of whom had experienced periodic paroxysms of sneezing followed by profuse rhinorrhea and nasal block, which occurred independently of season or climate. The intranasal structures were pale and waterlogged. Of the 11 persons yielding positive cutaneous reactions to various allergens, none had been benefited by allergic therapy. Only temporary improvement had followed numerous surgical procedures in 29 of the 40 cases. All the irradiated patients were free of polypi and secondary nasal infection. After topical cocainization a capsule containing 25 mg. of the radium element—total filtration being 0.5 mm. of silver and 1 mm. of brass—was placed in the middle and inferior meatuses of each nasal chamber for 2 hours—a dosage of 200 mg. hours. The morphologic and clinical response was uniformly striking—all the patients being appreciably benefited during the first 6 months. In a second communication (*Arch. Otolaryngol.*, 1933, **17**, 658) the same authors report that after 1 year, 52 per cent of these 40 irradiated patients were symptom-free; 20 per cent no longer had nasal block or watery discharge, although sneezing persisted in a moderate degree; 8 per cent were fairly comfortable; 10 per cent had received but little relief, and 10 per cent had not been benefited. No untoward sequelæ from their method of irradiation were observed. The authors frankly state that they regard the procedure as an empiric one and offer it solely as a useful adjunct in the many cases in which specific therapy had failed to correct the allergic state.

RADIOLOGY

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Actinomycosis of the Spine.—Actinomycosis is widely distributed over this country and is especially prevalent in the upper Mississippi Valley and the Northwest. Almost every region of the body has been

known to be affected, but the spine is one of the rarest sites known. TABB and TUCKER (*Am. J. Roent. and Rad. Therap.*, 1933, **29**, 628) report an instance in a man aged 33. Following a proved actinomycotic infection of the neck, numbness and paresis of the arms with pain in the back developed. The roentgenogram disclosed a perivertebral abscess and marked destruction of the 10th and 11th dorsal vertebræ, which, however, had not collapsed. A roentgenogram of the lungs also disclosed numerous foci in the upper half of the left lung, and actinomyces were found in the sputum. From a review of cases reported, Tabb and Tucker conclude that this disease usually attacks two or more vertebræ, that it attacks any part of the vertebra without preference for the body, and that the intervertebral spaces show little if any narrowing. Large perivertebral abscesses form early. Usually the lung is also affected when the spine is involved. Absence of collapse or kyphosis, despite extensive destruction of the vertebræ and the intact intervertebral spaces, aid in distinguishing actinomycosis from tuberculosis.

Hypertrophy of the Pyloric Muscle in Adults: A Distinctive Roentgenologic Sign.—Lesions at or near the pylorus are seldom difficult to discover with the Roentgen ray, but they are extraordinarily hard to identify specifically, for carcinoma, benign ulcer, syphilis and hypertrophy of the pyloric ring, which are the most common lesions here encountered, produce perplexingly similar manifestations. During recent months, however, KIRKLIN and HARRIS (*Am. J. Roent. and Rad. Therap.*, 1933, **29**, 417) have noted a roentgenologic phenomenon which appears to be peculiar to pyloric hypertrophy. The most obvious direct manifestation of uncomplicated hypertrophy is elongation of the pyloric canal. Not rarely the canal is eccentric in relation to the bulb. A definite mass corresponding to the defect cannot be felt. Hyperperistalsis is observed occasionally; gastric dilatation and retention of residue from the six-hour meal are rare. Thus far none of these signs is characteristic of pyloric hypertrophy, for similar manifestations are seen often in early scirrhous carcinoma, early syphilis, and prepyloric ulcer with spasm. But in pyloric hypertrophy Kirklin and Harris have noted a crescentic indentation of the bulbar base. It was evident in a series of 81 cases when the bulb was plainly depicted, accords with the morbid anatomy and has not been observed by the authors in other states of health or disease.

Diathermy Test for Sugar and Albumin in the Urine.—Because the present method of testing urine qualitatively for sugar and albumin is slow, messy and hence often neglected, KIMBLE (*Arch. Phys. Therap., X-ray, Rad.*, 1933, **14**, 237) has developed an electric device which eliminates these objections. The instrument consists of two small plates, insulated from each other, and connected through a shaft and cord to the terminals of a diathermy machine. It is designed to fit into any standard 20-cc. test tube. To test for albumin the tube is filled one-third full of urine, and a few drops of acetic acid added. The instrument is inserted and about 2000 ma. of current turned on. Albumin present is quickly coagulated and a white line appears between the terminals in from 2 to 5 seconds. To test for sugar 1 cc. of alkalin

bismuth subnitrate is added to the urine, and the same amount of current is employed. In a few seconds the solution between the two plates boils and is allowed to boil for ½ minute. If any sugar is present a black ring appears between the terminals.

Roentgen Diagnosis of Bone and Joint Tuberculosis.—Although he considers it obvious that criteria used in the roentgenologic diagnosis of tuberculosis are subject to diversified exceptions which make accurate interpretation extremely difficult, POMERANZ (*Am. J. Roent. and Rad. Ther.*, 1933, **29**, 753) enumerates the chief manifestations as follows: Synovitis and periarticular swelling, bone atrophy or sclerosis, bone production and destruction in epiphysis and metaphysis, narrowing of joint space, sequestration and the presence of cold abscesses or sinuses. Synovitis, periarticular swelling and bone atrophy are common to all arthritides and are only of corroborative value in the diagnosis of tuberculous arthritis. Sclerosis and production of bone occur in tuberculosis even in the absence of mixed infection, and, conversely, when sinuses exist bone production may be absent. Wedge or cone-shaped lesions are usually tuberculous. Kissing sequestra are common in tuberculosis. Narrowing of a joint space which occurs late in an infection, despite associated destructive changes, is strong presumption of the existence of tuberculosis. Complications, such as kyphosis, subluxation and sinus formation, occur in tuberculosis as well as other arthritids. Roentgenologically the presence of a cold abscess specifically identifies the process as tuberculous.

Roentgenologic Studies of the Intervertebral Disc.—According to COMPERE and KEYES (*Am. J. Roent. and Rad. Ther.*, 1933, **29**, 774), the nucleus pulposus, although genetically derived from the notochord, is not a vestigial remnant but an essential anatomic entity. It acts as a hydrodynamic ball bearing and axis of motion. Injury of the nucleus pulposus, whether primary or secondary to injury or to disease of the adjacent vertebral body, cartilage plate or annulus fibrosus, results in a decrease in normal function of the spine. Loss of nucleus pulposus material as a result of trauma or disease is probably one of the frequent etiologic factors of pain in the back and disability. Evidence indicates that degenerative or hypertrophic arthritis of the spine may result from loss of the nucleus pulposus, with subsequent erosion and narrowing of the fibrous and cartilaginous portion of the intervertebral disc. Prolapse of the nucleus pulposus into the spongiosa of the vertebral body is regarded by Schmorl as the commonest lesion of the spine. As a result of pressure by the weight of the body and by the tone of the muscles and ligaments, the nuclear material is extruded into the spongy bone, and the latter reacts to the invasion. The semifluid material is transformed into a cartilaginous nodule and the bone about it becomes sclerosed. If a large portion or all of the material is extruded the cushioning effect of the disc is lost, weight must be borne in part by the annulus fibrosus, and the intervertebral disc becomes thinner or disappears. As a result the adjacent vertebræ may become sclerosed and the lipping and spurs characteristic of osteoarthritis of the spine will be apparent in the roentgenogram.

NEUROLOGY AND PSYCHIATRY

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Lumbar Punctures in Psychotic Patients.—EPSTEIN and LOTT (*J. Nerv. and Ment. Dis.*, 1932, **76**, 593) state that the performance of lumbar punctures in psychotic patients is greatly facilitated by the use of sedatives, such as sodium amytal and nembutal. With the use of these sedatives, better coöperation is obtained for the lumbar puncture. Many of the difficulties in handling psychotic patients are overcome. Within an hour after the administration of the drug the patients are, as a rule, in a somnolent state, which may last from 4 to 8 hours. In this condition the patients offer no objections to the test and the element of fearfulness and anxiety is reduced to a minimum. There is little complaint of pain during the puncture. The patients are very drowsy afterward and are willing to lie on their backs in bed for the next twelve hours. No unpleasant memories of the procedure exist and consequently there is no opportunity for the wholesale dissemination of the "horrors" of the spinal test and engendering fear and antagonism toward the procedure among other patients. Another important advantage resulting from good coöperation between patient and the operator is the occurrence of fewer bloody (traumatic) taps.

The Depressive Reaction Types.—HARROWES (*J. Ment. Sci.*, 1933, **79**, 325) classifies the depressive reactions into the following groups: (1) Depressive reactions; (2) autogenous reactions; (3) recurrent depressions; (4) psychoneurotic depressions; (5) depressions with aversion; and (6) involutional types. The reactivity should be measured in terms of the patient's reaction to stimuli during the illness as well as the reaction to the etiologic factors. In the reactive group, besides the formal depression, were a lack of concentration, loss of interest, insomnia, loss of thought capacity, heightened sense of effort, headaches, forgetfulness. Self-accusatory trends were not prominent. The etiologic factors in the 14 cases reviewed were: sex and marital difficulties, 11 cases; work failures and difficulties, 2; and physical illness in1. The more cumulative the onset the more prolonged the psychosis. The more topical the affect, the less severe the psychosis. Constitutional and hereditary factors played a definite rôle, along with personality features such as unimaginativeness, materialism and rigidity. The reactive cases did not show any uniformity in the diurnal variation

of severity of symptoms, some being better in the evening and others in the morning. The retardation was not marked.

The autogenous depression presents characteristic differences from the reactive group which indicates a more sweeping type of disorder. The reactive group might be called partial reaction, and the autogenous group total reaction. Remorse and guilt ideas were more prominent and the affect embraces and involves more of the total personality of the individual. There is some distortion and a rut formation which is not seen in the reactive cases. A large proportion of the autogenous depressions showed recurrences.

The recurrent cases showed characteristic features, especially the tendency of attacks to become more severe as age advances. Otherwise, the picture presented has the same features as the single-attack autogenous depression, with the exception that there is more distortion and more rigidity present with evidence of an apprehensive, worrying disposition indicative of a more constitutionally depressive set than in simple cases. Guilt ideas were most prominent as well as agitation and tendency toward hypochondriasis.

The psychoneurotic depression usually developed on the basis of a neuropathic constitution with a characteristic makeup in which vasovegetative and neural disorders, including tachycardias, asthenias, sweat phenomena, asthma, tics, bed-wetting and nail-biting, were present. All degrees of anxiety were noted. The depression in this group is essentially topical and tends toward chronicity.

In the depressions with aversion definite paranoid trends were prominent along with the restriction of general interests and deterioration of affective response in any other direction. There is a reversal of the guilt component, and the presence of a rigid, dominating, obstinate personality-set. The prognosis in this group is poor.

The involutional depression with a well known syndrome of peevishness, hypochondria and nihilistic ideas, and restriction of affect were most typical. Sudden onset, impulsive suicidal attempts were frequently noted.

In summarizing the depressive reactions, there appears to be the following groups: (1) Where a real life-situational, dynamic cause can be seen; (2) another where the cause is more entirely constitutional; (3) a group with a special affectivity handicap in the form of a psychosis; (4) a group with aversion, where the prognosis is bad; and (5) a special type of agebound depressions with a better prognosis than might be expected. The prognosis in the reactive group seems very much a question of balancing the trauma and the personality assets. In the autogenous cases the personality alone can be focused on. Emphasis is laid on rigidity of the personality as an ominous sign. The type of onset—cumulative or catastrophic—and the extent to which the affect is bound to the etiologic topics are of prognostic significance.

EDITORIAL COMMENT.—This is a most excellent article. Perhaps simpler classifications would be of value, such as the one proposed by Gillespie consisting of two main groups—the reactive and the autonomous, with a subgrouping to include involutional cases.

PATHOLOGY AND BACTERIOLOGY

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Agglutination Experiments as Evidence of the Diversity of Non-hemolytic Streptococci.—CROWE (*J. Inf. Dis.*, 1933, **52**, 192) suggests four criteria for the differentiation of various races of bacteria: (1) Cultural and microscopic characters; (2) disease producing characters; (3) special morphologic and biochemical characters; (4) serologic characters. The author's medium demonstrates cultural and gross morphologic characters. The medium is chocolate-colored, glassy and opaque, and is composed of 75 per cent of heated, defibrinated blood. Differences in the amount of H_2O_2 produced are shown by the degree of greenish discoloration surrounding the colonies. The microscopic characters are variable according to environment, and, therefore, are of little value except under exactly similar conditions of growth. The second criterion—disease producing characters—is not sufficient to distinguish microbes, since different organisms are responsible for the same clinical conditions. The third criterion is based on special media and fermentation characters which are not wholly reliable. By agglutination tests with monovalent rabbit serums, criterion 4, it is shown that certain streptococci differing on cultural characters, but similar in fermentation are heterologous in type, indicating that they are definitely distinct organisms since two of three criteria are satisfied. The differences between the varieties of non-hemolytic streptococci cannot reasonably be ascribed to mutation but are to be considered fundamental.

Syphilis of the Pulmonary Artery.—KARSNER (*Arch. Int. Med.*, 1933, **51**, 367) reviewed the literature on syphilis of the pulmonary artery and reports a case. Peck had previously analyzed the cases of syphilis of pulmonary artery up to 1927, accepting only 12. The author collects 16 cases. His case presented difficulty clinically, in that there was reasonable evidence of syphilitic aortitis, but the presence of a to-and-fro murmur in the right carotid, absence of pulse in arteries of the arm and a systolic murmur heard in the pulmonic area presented a confusing picture. After autopsy, further study of previous roentgenograms revealed a shadow at the right hilus, indicative of dilatation of the right pulmonary artery. At autopsy the significant findings were marked syphilitic arteritis of the arch of the aorta and the main trunk of the pulmonary artery. There was a fusiform dilatation and small saccular aneurysms of the aorta with syphilitic arteritis of the three branches from the arch. The innominate and subclavian arteries were completely thrombosed and recanalized. The main pulmonary

artery presented a fusiform dilatation, with dilatation of the right branch and thrombosis with recanalization of the left. Microscopic evidence was definitely that of a specific process, presenting the productive cicatricial syphilitic lesions as seen in syphilitic mesaortitis. The author does not believe this process to have spread from the aortitis because of the part of the aorta in closest contact with the pulmonary artery was free from pathologic lesions.

Selective Action of Crystal Violet and of Brilliant Green on Bacteriophages.—For their experiments WELLS and SHERWOOD (*J. Inf. Dis.*, 1933, **52**, 209) used six lytic principles, two for Gram-positive bacteria and four for Gram-negative bacteria. The mixtures of dye and bacteriophage were made in dilutions of 1 to 2500 to 1 to 10,000, and incubated at 37° C. The lysin against Gram-positive organisms was found to be inhibited by crystal violet in all dilutions within 48 hours. The lytic agents against Gram-negative organisms were never inhibited above 1 to 5000. The inhibitive property of brilliant green was extremely variable, but distinct with one phage of colon bacillus in particular. After incubation the activity of the phage was tested in high dilutions, *i. e.*, above that at which the dye was inhibitive on bacteria. The demonstration suggests that there is a correlation between the selective action of crystal violet on bacteria and their respective phages.

Desiccation and Preservation of Infectious Laryngotrachitis Virus.—A method for the preservation of virus in tracheal exudates by drying is described by GIBBS (*J. Bact.*, 1933, **25**, 245). The desiccation of tracheal exudate *in vacuo* preserves the virus indefinitely because the moisture necessary for bacterial decomposition and the oxygen essential for oxidation and enzyme action are removed. The material is kept at a low temperature just above freezing until completely dehydrated, and protected from air, moisture and direct sunlight. A large desiccator is used and is sealed with a mixture of gum rubber, paraffin and vaseline. Acid phosphoric anhydrid is used as dehydrating agent. The air is evacuated to a vacuum of 300 microns mercury daily for 4 or 5 days, being kept in the ice box in the intervals. The tubes of exudate are then sealed with paraffin and kept in the ice box. Three strains of virus were tested; those desiccated at less than 300 microns were preserved not more than 1 year, while those treated at more than 300 microns were virulent up to 450 days.

Sclerosis of Pulmonary Artery and Arterioles.—SOKOLOFF and STEWART (*Arch. Int. Med.*, 1933, **51**, 413) report a case of sclerosis of pulmonary arteries. Their record includes a 7-year period of observation of the patient, and a careful analysis of the case, in which they excluded the possibility of syphilitic infection by clinical, laboratory and pathologic investigations. The clinical diagnosis was not made until late in the disease, when the typical sign of Ayerza's syndrome became evident. Postmortem examination revealed a dilated and hypertrophied heart on both sides, with passive congestion and anasarca present throughout the body. The pulmonary artery and its branches

presented interesting features. Flat, grayish, firm plaques were seen, increasing in frequency toward the periphery, producing marked sclerosis of this arterial system. They suggest three pathogenic factors: (1) An attack of influenzal pneumonia 1 year before the onset of symptoms is possibly of some significance; (2) the patient received repeated injections of epinephrin to relieve periodic attacks of asthma, most of which were, however, unsuccessful; (3) the presence of an old fracture of rib, which might have caused local injury or stimulation of nerves resulting in the above lesions. They review experimental work to support each one of these factors.

HYGIENE AND PUBLIC HEALTH

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Lobar Pneumonia in Massachusetts: Methods and Results of Pneumococcus Type Determination, 1931–1932.—According to HEFFROM and VARLEY (*Am. J. Pub. Health*, 1932, **22**, 1230), pneumococcus typing is being requested by increasing numbers of physicians in Massachusetts. During the past winter all 32 (Cooper) types of pneumococci excepting Types XXV and XXXII were found. There was no especial geographical distribution evident of any of the types found. Multiple cases of lobar pneumonia occurring in the same family at approximately the same time were very uncommon. The Krumwiede, Sabin and tube agglutination methods of typing were and still are largely used, and were found to be over 99 per cent accurate when definitely positive. The Sabin method of typing has given a greater number of accurate positive typings in a shorter period of time than any other method studied, and is a method readily learned by technicians inexperienced in this work. Of 789 specimens typed at the State Bacteriological Laboratory during the 11 months, September 1, 1931, to July 31, 1932, the type of pneumococcus found was checked in 94.6 per cent of the cases by a second method of typing or from a culture of the organism. The various sub-types (Types IV to XXXII) were found more frequently during the 6 winter and spring months, December to May, than during the warmer months. In view of the results to date, and until conclusive proof to the contrary is obtained, it is felt that every type determination done by the Krumwiede, Sabin or tube agglutination method should be checked by some other method of typing. Typing the organism obtained from cultures of the mouse heart's blood affords the most valuable means of checking.

Plasmochin in Malaria Prevention.—The results of two experiments conducted by BAKER and GILL (*U. S. Pub. Health Rept.*, 1932, **47**, 2245), covering 2 consecutive years, suggest that plasmochin compound in a dosage of 1 to 2 tablets per week (each tablet containing 0.01 gm. plasmochin and 0.125 gm. quinin sulphate), when administered to all the inhabitants of a district, will materially lessen the incidence of malaria. Such a dosage is both safe and convenient. If further experience confirms these results, it would seem that a valuable addition has been made to the present methods of malaria control, which therapeutic control may be further enhanced through scientific chemical study of the potentialities embraced in plasmochin.

The Fernald Plan for the Examination of Retarded School Children.—DAYTON (*New England J. Med.*, 1932, **207**, 913) states that the present high position which Massachusetts occupies in the care of the mentally deficient is due largely to the pioneer work of Dr. W. E. Fernald. Over 30 years ago he realized the urgent need for public recognition of the problem of mental defect and the necessity for early diagnosis of cases showing mental retardation. His first plan was the creation of an out-patient department. Later, he conceived the thought of projecting the out-patient examination into the public school system, and by means of a traveling clinic to visit each school, conducting a comprehensive examination of the retarded children therein. The first of these units was inagurated in 1914, and the second in 1917. The "Ten-point Scale Examination" presents a detailed picture of the retarded child, giving the sum total of his characteristics and reactions apart from his intelligence. The personnel of the traveling clinic unit consists of a psychiatrist, a psychologist and a social worker. In addition, the school provides a school teacher, a school nurse and a visiting teacher who assist in certain phases of the examination. Since the inauguration of the school clinic system in 1914, a total of 51,205 examinations of retarded children have been conducted. Approximately 41,000 of this total are first examinations, and 10,000 are reëxaminations. These figures show the magnitude of the problem of the retarded children within the public schools, and demonstrate the volume of work which has been accomplished by the traveling school clinics.

Further Attempts at Experimental Infection of Man With a Bovine Strain of Brucella Abortus.—MORALES-OTERO (*J. Inf. Dis.*, 1933, **52**, 54) states that in spite of the little prevalence of spontaneous human infection in regions where infectious abortion in cattle is common, a fever in man similar to undulant fever may be produced by artificial inoculation with cultures of Br. abortus. His previous experiments left no doubt that strains of porcine origin in particular are decidedly pathogenic for man. They not only cause infection when injected through abraded skin, but are also able to penetrate through the gastro-intestinal canal when fed in sufficient quantity. In contrast to this, it has not been possible to produce human infection by feeding a strain of bovine origin, isolated in Puerto Rico. A family consisting of 3 members volunteered to ingest for 6 weeks the infected milk of a

cow suffering from infection with Br. abortus. At the end of this period, none of the members had at any time shown any symptoms of the disease, and their blood cultures and blood agglutination tests remained persistently negative for Br. abortus. Two other volunteers, inoculated, 1 through normal and the other through abraded skin, with a strain isolated from infected cow's milk, presented no symptoms of the disease, and their blood cultures were persistently negative for Br. abortus. In the blood of the latter of the 2 persons a transitory positive agglutination of the organism (in a 1 to 40 dilution) was observed during the third and fourth weeks of the experiment. Hence, the pathogenicity for man of bovine strains must be low, an assumption supported by the wide distribution of infectious abortion in cattle with no corresponding spontaneous occurrence of undulant fever in the human being. On the other hand, reports from southern Rhodesia and Denmark seem to indicate that human infection in those countries is frequently due to the bovine type of bacillus. Further work is necessary to study the various pathogenic and non-pathogenic races of Brucella and to determine if there are any factors that might lead to an exaltation of virulence in those that are normally considered non-pathogenic.

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Typhus Fever.—CEDER, DYER, RUMREICH and BADGER (*U. S. Pub. Health Rep.*, 1931, **46**, 3103) were unable to transmit typhus to animals by direct biting of fleas, but succeeded by the inoculation of crushed fleas and by the use of fresh feces. DYER, WORKMAN and RUMREICH (*Ibid.*, 1932, **47**, 2370) report the recovery of typhus virus from rat fleas in different parts of the world. In the present report, the rats were trapped in the United States on premises where cases of endemic typhus in man had occurred. The virus was recovered from rats by passing through guinea-pigs. Identification was completed by various pathologic and biologic tests.

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